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Hodgkin lymphoma

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Abstract | Hodgkin lymphoma (HL) is a B cell lymphoma characterized by few malignant cells and numerous immune effector cells in the tumour microenvironment. The incidence of HL is highest in adolescents and young adults, although HL can affect elderly individuals. Diagnosis is based on histological and immunohistochemical analyses of tissue from a lymph node biopsy; the tissue morphology and antigen expression profile enable classification into one of the four types of classic HL (nodular sclerosis, mixed cellularity, lymphocyte-depleted or lymphocyte-rich HL), which account for the majority of cases, or nodular lymphocyte-predominant HL. Although uncommon, HL remains a crucial test case for progress in cancer treatment. HL was among the first systemic neoplasms shown to be curable with radiation therapy and multiagent chemotherapy. The goal of multimodality therapy is to minimize lifelong residual treatment-associated toxicity while maintaining high levels of effectiveness. Recurrent or refractory disease can be effectively treated or cured with high-dose chemotherapy followed by autologous haematopoietic stem cell transplantation, and prospective trials have demonstrated the potency of immunotherapeutic approaches with antibody–drug conjugates and immune checkpoint inhibitors. This Primer explores the wealth of information that has been assembled to understand HL; these updated observations verify that HL investigation and treatment remain at the leading edge of oncological research.

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https://doi.org/10.1038/s41572-020-0189-6

Hodgkin lymphoma (HL) is an uncommon neoplasm that occurs primarily in young adults and, albeit less frequently, in elderly individuals. HL has several remarkable characteristics that are nearly unique among human malignancies, including young age of onset; rarity of malignant cells, which are large multinucleated cells derived from B lymphocytes (known as Hodgkin and Reed–Sternberg (HRS) cells) and are usually present within a microenvironment rich in immune effector cells; a high cure rate, even when the patient presents with advanced metastatic spread; and a particular sensitivity to radiation therapy. At least 90% of patients present with the classic form of the disease (cHL) in which HRS cells expressing the cell surface CD30 antigen (also known as tumour necrosis factor (TNF) receptor superfamily member 8) are scattered throughout a microenvironment comprising inflammatory cells, lymphocytes and macrophages[1,2]. cHL includes four subtypes, nodular sclerosis HL (NSHL), mixed cellularity HL (MCHL), lymphocyte-rich HL (LRHL) and lymphocyte-depleted HL (LDHL), although in 5% of patients with cHL, a subtype cannot be specified, usually because of insufficient material for full analysis. Epstein–Barr virus (EBV) plays a part in the aetiology of HL in at least some patients, as suggested by the presence of EBV within the malignant cells (known as EBV tumour status), which varies considerably across the cHL subtypes, ranging from ~75% in MCHL and LDHL[3] to <20% in NSHL and LRHL. A minority of patients, ~10%, present with nodular lymphocyte-predominant HL (NLPHL), in which a microenvironment of mature lymphocytes is punctuated by malignant cells (lymphocyte-predominant (LP) cells, large cells expressing B lymphocyte antigen CD20)[1,4] (FIG. 1).

On presentation, cHL is usually present in supradiaphragmatic lymph nodes. It then spreads to contiguous lymph nodes, eventually reaches the spleen, and then disseminates to extranodal deposits in bone marrow, bone, lung and liver. Optimal treatment is chosen based on standard staging, and cure rates exceeding 90% for limited stage disease[5–9] and 80% for advanced disease[10–14] are routinely achieved; however, physicians need to also carefully consider ways to minimize irreversible, often late-onset, treatment-related toxicity, such as second malignancy induction or cardiac dysfunction, while preserving treatment effectiveness. Even when HL does not remit or recurs despite optimized primary treatment, it can still often be cured with administration of high-dose chemotherapy supported by autologous haematopoietic stem cell transplantation (ASCT) in at least 50% of patients[15,16].

In this Primer, we focus on cHL with a brief description of NLPHL. We explain how insights into the basic biology of the malignant cells have contributed to

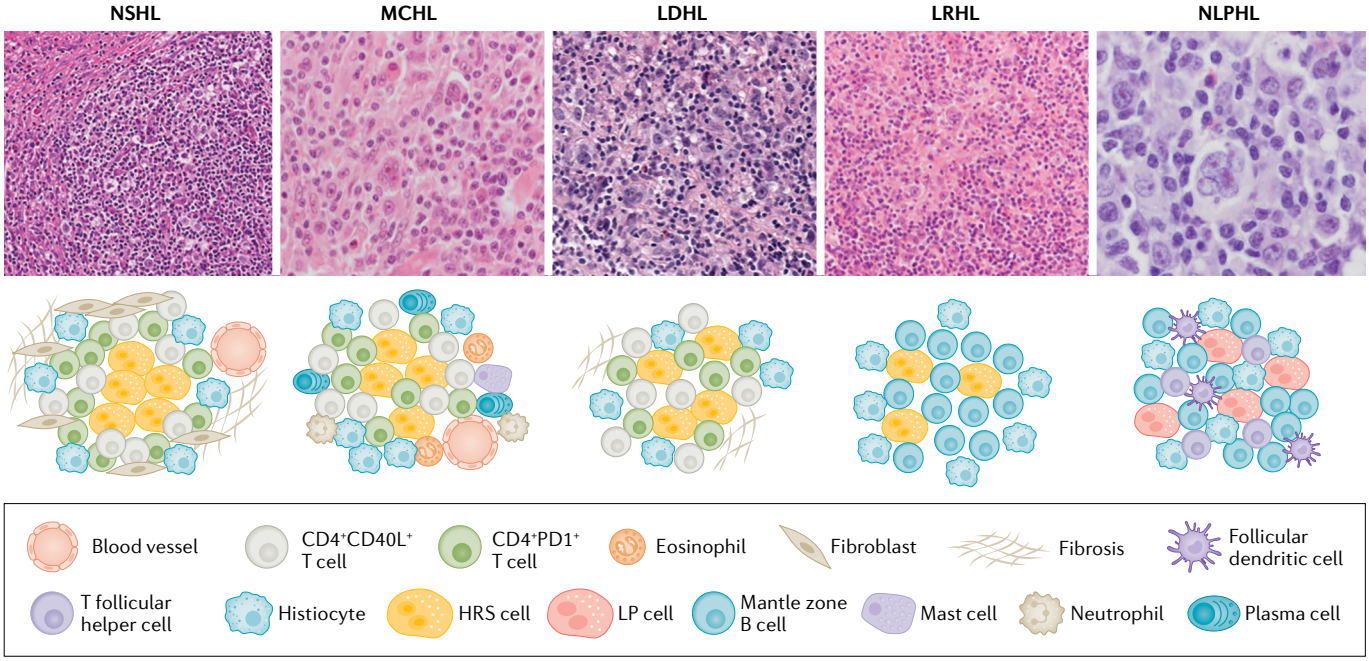

Fig. 1 | **Morphological and cellular characteristics of Hodgkin lymphoma.** Histology images (top row) and corresponding drawings (bottom row) show the cell types of the tumour microenvironment (TME) of the four subtypes of classic Hodgkin lymphoma (cHL) and the nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL). The TME in cHL demonstrates a variable cellularity that is different in each subtype. In nodular sclerosis Hodgkin lymphoma (NSHL), the TME is specifically characterized by fibroblast-like cells and fibrosis (original magnification ×20). In mixed cellularity Hodgkin lymphoma (MCHL), the TME consists of a polymorphous reactive infiltrate with B cells and T cells, neutrophils, histiocytes, plasma cells and mast cells (original magnification ×40). In lymphocyte-depleted Hodgkin lymphoma (LDHL), the TME is usually composed of histiocytes and irregular fibrosis (original magnification ×40). In lymphocyte-rich Hodgkin lymphoma (LRHL), the TME is variable but usually consists of histiocytes and lymphocytes (original magnification ×20). The TME of NLPHL is similar to that of LRHL, although in NLPHL it is rich in follicular dendritic cells (original magnification ×60). HRS, Hodgkin and Reed–Sternberg; LP, lymphocyte-predominant.

accurate diagnosis and, even more importantly, have led to the introduction of new agents including antibody–drug conjugates and immune checkpoint inhibitors. We describe optimized approaches to limited-stage and advanced-stage disease and to refractory or recurrent disease. On the basis of the global annual incidence of HL (100,000 cases)[17] and past and current cure rates exceeding 50%, it is reasonable to project that, as of 2020, in the last 50 years, >1 million individuals worldwide have been cured of HL. How this result was achieved, what burden of late-onset complications these individuals must live with and how even better results will be achieved in the future is an exciting story that is continuing to unfold.

Epidemiology

Incidence and prevalence

The overall incidence of HL is low, with an average annual age-adjusted incidence in populations of European ancestry of ~2–3 per 100,000 individuals[18]; nevertheless, HL is one of the most common cancers diagnosed in young adults in these populations. The trimodal age-specific incidence pattern varies by histological subtype, EBV tumour status and demographic characteristics[2,19,20] (FIG. 2). In populations of European ancestry, the major incidence peak of HL occurs among adolescents and young adults (AYAs) in the age range 15–35 years, with a slightly higher incidence in females than in males, and 60–70% of patients have EBV-negative NSHL[21]. The risk of developing HL, particularly in the AYA age group, is higher in economically developed regions (FIG. 3) and among individuals of high socio-economic status than in low-income areas, with the incidence increasing with economic development over time[20]. Historically, the likelihood of developing cHL in the AYA population has been inversely associated with the number of siblings[22], suggesting increased susceptibility due to lack of early childhood exposure to specific infections or to microorganisms in general, possibly affecting normal immune response maturation. Consistent with this hypothesis, allergic diseases such as asthma and eczema (also known as atopic dermatitis), which may also be linked to lack of exposure to microorganisms in childhood[23], have been associated with an increased risk of developing cHL in the AYA population[24].

The two small HL incidence peaks in children (<15 years of age) and elderly adults (>50 years of age) are composed mainly of patients with MCHL, with a high prevalence of EBV-positive cases (up to 70% of elderly adults with cHL) and are associated with low socio-economic status, non-European ethnicity and male sex[19–21]. A history of infectious mononucleosis (which is mostly caused by EBV infection) is strongly

associated with an increased risk of EBV-positive, but not EBV-negative, cHL[25,26]. NLPHL, LRHL and LDHL are too rare to be studied in large numbers and do not have distinctive age-related risk or ethnicity-associated incidence patterns, although all types of cHL occur more often in males than in females[27,28], and NLPHL shows evidence of familiality[29].

Mortality and risk factors

As increasingly effective treatments have become available for HL, any potential differences in mortality related to HL subtype have largely disappeared. However, modestly worse mortality is observed in male patients than in female patients[30], and much worse mortality is observed in elderly patients, especially those of >70 years of age, than in young people[31]. In the USA, mortality from HL is higher in Black and Hispanic individuals than in non-Hispanic white individuals, possibly owing to differences in access to medical care[32].

In people with HIV infection, cHL is one of the most common non-AIDS-defining cancers and is almost always EBV-positive[33,34]. Studies regarding HIV infection among risk factors for the development of lymphomas have shown that people with HIV infection or AIDS are at increased risk of HL since the introduction of highly active antiretroviral therapy (HAART)[3,33]. One possible explanation for this increased incidence may relate to the role of EBV and the participation of cells in the tumour microenvironment (TME) in the development of cHL. Severely immunosuppressed individuals are known to have a high risk for EBV-associated aggressive non-Hodgkin lymphomas, which was reflected in the early years of the AIDS epidemic before the introduction of HAART. However, with the widespread availability of HAART, HIV-infected individuals are now only moderately immunosuppressed and, therefore, have a more immunologically competent cellular microenvironment present within lymph nodes, leading to a shift in the type of lymphoma away from EBV-associated non-Hodgkin lymphoma to EBV-associated HL. Consistent with this hypothesis are the observations that HIV-associated HL is typically also EBV-associated and that cHL occurs much less frequently in association with AIDS if the $CD4^+$ T cell count is <50 cells per mm^3. With the improved immune competence achieved as HAART has become increasingly widespread, AIDS-associated cHL has increased in incidence and shifted from mostly MCHL to NSHL[35], possibly reflecting changes in TME cellular interactions.

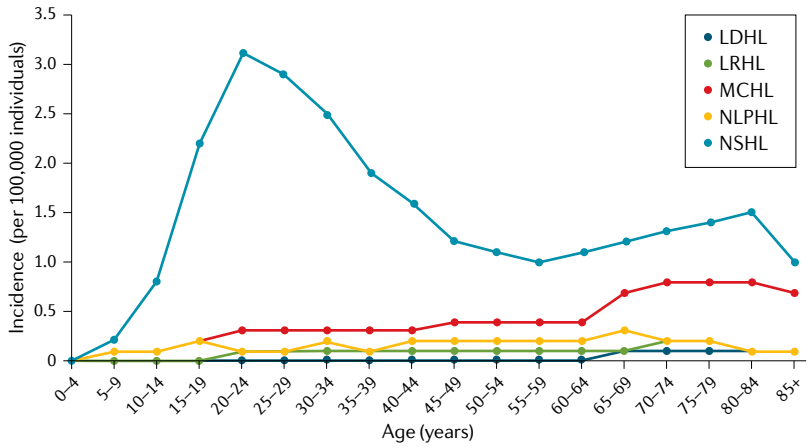

Fig. 2 | **Relationship between age and subtype of Hodgkin lymphoma.** The graph is based on 2000–2015 average annual age-specific incidence rates from the Surveillance, Epidemiology, and End Results (SEER) Program and shows the early and late peaks (the childhood peak cannot be detected on this scale) in nodular sclerosis Hodgkin lymphoma (NSHL) and the late peak in mixed cellularity Hodgkin lymphoma (MCHL). LDHL, lymphocyte-depleted Hodgkin lymphoma; LRHL, lymphocyte-rich Hodgkin lymphoma; NLPHL, nodular lymphocyte-predominant Hodgkin lymphoma.

Genetic risk factors

cHL is strongly heritable, especially in AYAs, with a very high (~100-fold) risk in identical twins compared with fraternal twins[36]. Certain HLA alleles have long been known to be linked to increased HL risk, with HLA class I alleles associated with EBV-positive cHL and HLA class II alleles with EBV-negative cHL[37]. Genome-wide association studies in populations of European ancestry have identified 18 genetic risk variants primarily in immune related genes[38,39]. Variants in *GATA3*, *IL13* and genes controlling the expression of HLA class II molecules are strongly associated with EBV-negative NSHL in AYAs[38]. The variant rs6903608 is the polymorphism most significantly (P value up to 10^{-300}) associated with development of this type of HL and is located near *HLA-DRB** (REF.[40]). Several genetic risk variants in HLA-A*01 and HLA-A*02 risk alleles[41] (encoding HLA class I molecules that may alter the cytotoxic $CD8^+$ lymphocyte response to EBV[42]) are associated exclusively with EBV-positive cHL. Another genetic variant in *TCF3* is inversely related to overall cHL risk and is associated with increased expression of the transcription factor E2-α protein (also known as transcription factor 3, TCF3) in B cells from healthy individuals[38], linking risk and tumour biology. *TCF3* maintains the B cell phenotype and is downregulated in HRS cells[38]; thus, the presence of this genetic variant and the resultant increased expression of TCF3 is protective. Five recently identified loci have been associated with increased overall HL risk; functional studies have demonstrated that these and the other risk loci mentioned above influence regulatory regions in germinal centre B cells, $CD4^+$ T cells, $CD8^+$ T cells and $CD4^+$ thymocytes (immature T lymphocyte precursors present in the thymus) and are associated with pathways in the germinal centre reaction (the generation of antigen-specific B cell clones), T cell differentiation and function, and nuclear factor-κB (NF-κB) activation[39], providing further evidence of a link between genetic susceptibility and tumour biology. Although there is no evidence of shared genetic susceptibility with 20 common infections[39], HL has genetic risk factors in common with autoimmune disease and atopy[43].

Mechanisms/pathophysiology

Tumour cells

Malignant HRS cells in cHL and LP cells in NLPHL are thought to exploit immune escape mechanisms and deficiencies in host immunity, and they recruit an immune-modulatory microenvironment that makes HL a unique neoplasm amongst all cancers. The paucity

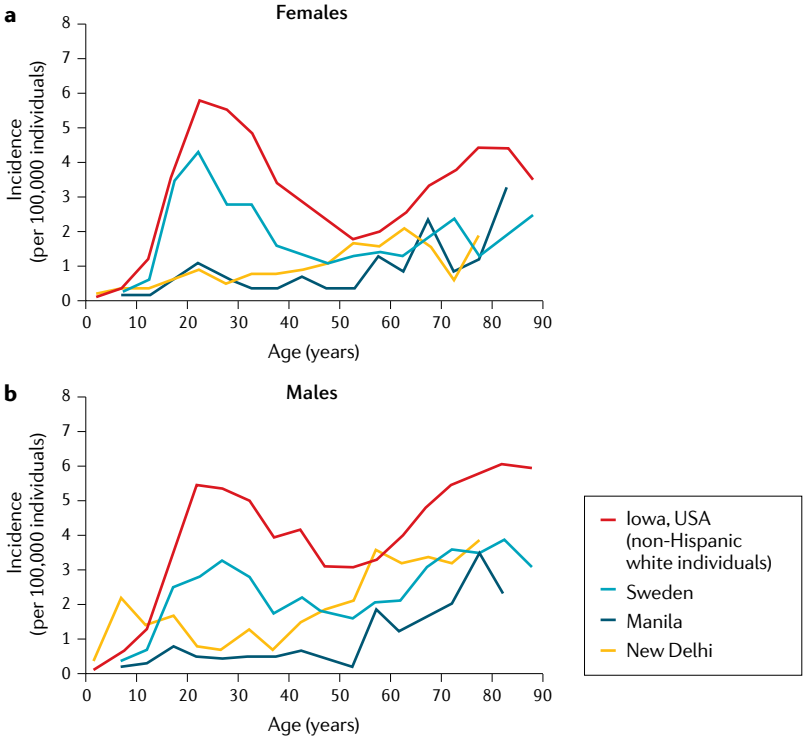

Fig. 3 | **Annual age-specific incidence of Hodgkin lymphoma in different regions.** Average annual age-specific incidence of Hodgkin lymphoma (all subtypes combined) per 100,000 female (panel **a**) and male (panel **b**) individuals diagnosed during the period 2003–2007 in two economically developed regions (Iowa, USA, and Sweden) and two developing regions (New Delhi and Manila). Data from REF.[2].

of the malignant cells in the TME imposes major challenges to the study of malignant cell biology and disease modelling, both in vitro and in vivo. As a result, most biology studies are based on the characterization of primary biopsies from patients with HL and a handful of HL-derived cell lines, whereas ex vivo models that accurately reproduce HL disease biology have not been reliably identified[44]. Moreover, our current knowledge about molecular mechanisms and pathophysiology is mainly based on studies in cHL, although recently some insight has been gained in NLPHL through sequencing and gene expression profiling[45,46].

HRS cells seem to originate in germinal centres[47,48] and have a gene expression pattern similar to that of $CD30^+$ extrafollicular B cells[49]. These cells typically display features suggesting a loss of B cell phenotype: although it has been demonstrated that they are of B cell origin, they lack typical B cell lineage markers (for example, B lymphocyte antigen CD19, B cell antigen receptor complex-associated protein α-chain (also known as CD79A) and immunoglobulin expression) (see Diagnosis, screening and prevention)[50,51]. Recently developed molecular techniques, in particular genome-wide analyses, such as sequencing of micro-dissected HRS cells and circulating tumour DNA (ctDNA; that is, cell-free tumour DNA circulating in the peripheral blood), have led to a more refined molecular characterization of HRS cells[52–57]. Moreover, gene expression profiling techniques, immunohistochemistry and flow and mass cytometry techniques have helped to delineate a more detailed understanding of the TME and elucidate cellular crosstalk[58–63]. Of clinical importance, some of these novel insights have provided the rationale for treatment approaches (for example, monoclonal antibodies to antigens expressed by the tumour cells such as brentuximab vedotin, targeting programmed cell death protein 1 (PD1) signalling and chimeric antigen receptor (CAR) T cell therapies) that are now part of standard care or are being tested in current clinical trials[64,65].

Loss of B cell phenotype. HRS cells are characterized by a nearly complete loss of classic B lineage markers, such as CD19, B lymphocyte antigen CD20, B cell receptor CD22, CD79A and B cell antigen receptor complex-associated protein β-chain (also known as CD79B)[51], and the expression of lineage-inappropriate markers of T cells (for example, T cell surface antigen CD2, T cell surface glycoprotein CD3 and T cell surface glycoprotein CD4), myeloid cells (for example, the cell-surface glycan CD15 antigen) and dendritic cells (for example, CD83 antigen) can further obscure the B lymphocyte origin[66,67]. Despite this uncharacteristic mixed expression phenotype, molecular analysis has demonstrated that HRS cells harbour clonal rearrangements of hypermutated, class-switched immunoglobulin genes, which result from both the neoplastic nature of the disease and its B cell derivation. Moreover, activation-induced cytidine deaminase (AID)-driven somatic hypermutation was shown to result in non-functional immunoglobulin genes and lack of expression of cell surface B cell receptor (BCR)[48]. Although unproductive rearrangements of BCR genes typically trigger apoptosis of these germinal centre B cells under physiological circumstances, the most widely accepted pathogenesis model of cHL postulates that HRS cells are rescued from apoptosis through constitutive activation of signalling pathways driven, in part, by AID-related somatic mutations, infection with EBV or microenvironmental signalling, as discussed below.

The loss of the B cell phenotype is probably caused by a combination of promoter hypermethylation that dysregulates the expression of genes required for T cell and B cell differentiation and epigenetic silencing of key regulators of B cell differentiation. Examples include deregulation of the transcriptional repressors DNA-binding protein inhibitor ID2 and musculin (also known as ABF1), leading to repression of TCF3[68], and of neurogenic locus notch homologue protein 1 (NOTCH1)[69,70] and aberrant expression of the polycomb complex proteins, which regulate chromatin remodelling[71,72]. Although almost all cases of HL are of B cell lineage, rare clonal rearrangements of genes encoding the T cell receptor have also been reported, suggesting that a very small proportion of cases overlap with T cell lymphomas at the molecular level, although whether such cases represent true HL or an otherwise unclassifiable non-Hodgkin T cell lymphoma remains controversial[73].

NF-κB signalling. Multiple genes may become mutated or dysregulated in HL, typically altering pathways involved in cell survival and immune escape (TABLE 1). Somatic gene mutations leading to constitutive

Table 1 | **Genes and proteins frequently dysregulated in Hodgkin lymphoma and promoting HRS cell survival**

Gene	Protein	Mechanisms of action	Refs
NF-κB signalling activation			
TNFRSF8 (also known as *CD30*)	TNF receptor superfamily member 8 (also known as CD30)	Expression of these TNF receptor family members by HRS cells induces paracrine activation of NF-κB, thereby supporting HRS cell survival	74
CD40L	CD40 ligand		
TNFRSF13B (also known as *TACI*)	TNF receptor superfamily member 13B (also known as CD267)		
TNFRSF17	TNF receptor superfamily member 17		
TNFRSF11A (also known as *RANK*)	TNF receptor superfamily member 11A		
EBV *LMP1*	Latent membrane protein 1	TNF receptor mimicking leads to activation of the NF-κB pathway, thereby supporting HRS cell survival in EBV-positive cHL	75–77
REL	Proto-oncogene c-Rel	Gene amplifications, gains and structural rearrangements lead to upregulation of NF-κB	52,78,260
BCL3	B cell lymphoma 3 protein		
MAP3K14	Mitogen-activated protein kinase kinase kinase 14		
NFKBIA	NF-κB inhibitor-α	Inactivating mutations of these negative regulators lead to increased expression of NF-κB	79–82,261
NFKBIE	NF-κB inhibitor-ε		
TNFAIP3	TNF-induced protein 3		
JAK–STAT signalling activation			
STAT3	Signal transducer and activator of transcription 3	Activating mutations, gene amplifications, gains and structural rearrangements lead to constitutive activation of JAK–STAT pathways, promoting cell proliferation	55–57,83–86, 110,262
STAT5A	Signal transducer and activator of transcription 5A		
STATB	Signal transducer and activator of transcription 5B		
STAT6	Signal transducer and activator of transcription 6		
JAK2	Tyrosine-protein kinase JAK2		
PTPN1	Tyrosine protein phosphatase non-receptor type 1		
SOCS1	Suppressor of cytokine signalling 1		
BATF3	Basic leucine zipper transcriptional factor ATF-like 3		
IL13	IL-13	Autocrine and paracrine activation of JAK–STAT pathways support enhanced cell growth	87,88
IL13RA2 (also known as *IL13R*)	IL-13 receptor subunit α2		
IL21	IL-21		
IL21R	IL-21 receptor		
PI3K–AKT signalling activation			
PDGFRA	Platelet-derived growth factor receptor-α	Activation of signal transduction pathways involved in cell adhesion, proliferation and extracellular matrix remodelling	91–93
DDR2	Discoidin domain-containing receptor 2		
NTRK1 (also known as *TRKA*)	High-affinity nerve growth factor receptor (also known as tyrosine kinase receptor A (TRKA))		
NTRK2 (also known as *TRKB*)	BDNF/NT-3 growth factor receptor (also known as TrkB tyrosine kinase (TRKB))		
Acquired immune escape			
B2M	β_2-microglobulin	Somatic loss-of-function mutations abrogate assembly of HLA class I molecules, which results in loss of functional surface expression	53,105,107, 108,111,263
CIITA	MHC class II transactivator	Chromosomal rearrangements of the master transcriptional regulator of HLA class II molecules expression lead to loss of effective antigen presentation	
CD58	Lymphocyte function-associated antigen 3 (also known as CD58)	Somatic mutations and deletions result in decreased cytotoxic T cell and NK cell recognition	
CD274 (also known as *PDL1*)	Programmed cell death 1 ligand 1 (PDL1)	Genomic amplification and rearrangements lead to overexpression of these PD1 ligands,	
PDCD1LG2 (also known as *PDL2*)	Programmed cell death 1 ligand 2 (PDL2)		

AKT, RACα serine/threonine protein kinase; cHL, classic Hodgkin lymphoma; EBV, Epstein–Barr virus; HRS, Hodgkin and Reed–Sternberg; JAK, Janus kinase; NF-κB, nuclear factor-κB; NK, natural killer; PI3K, phosphatidylinositol 3-kinase; STAT, signal transducer and activator of transcription; TNF, tumour necrosis factor.

activation of NF-κB are one of the major molecular hallmarks of cHL and play a central part in pathogenesis; however, cytokines, chemokines and ligands associated with interleukins and TNF receptors expressed in the TME can also extrinsically activate the NF-κB pathway[74]. In aggregate, downstream effects of NF-κB activation include regulation of anti-apoptotic factors, expression of pro-inflammatory cytokines and B cell reprogramming. In about 30–40% of patients with cHL, and in particular MCHL, the HL is associated with EBV infection[75], and the viral oncoprotein latent membrane protein 1 (LMP1), mimicking an activated TNF receptor, can also activate the NF-κB pathway, thereby supporting HRS cell survival in EBV-positive cHL[76,77]. Genomic gains and amplifications of *REL* have been found in up to 70 % of patients with cHL and have been reported to cause protein overexpression[52,78]. Inactivating mutations of negative regulators of NF-κB (for example, *NFKBIA* and *TNFAIP3*) are another major mechanism of NF-κB pathway activation[79,80]. *TNFAIP3* encodes TNF-induced protein 3 (also known as A20), which functions as a post-translational modifier of NF-κB pathway members and negatively regulates the NF-κB pathway. Deletions and somatic mutations of this tumour suppressor gene have been reported in higher frequencies in EBV-negative cHL than in EBV-positive cHL, suggesting that *TNFAIP3* mutations and EBV-driven pathogenesis may converge through similar phenotypic effects including NF-κB pathway activation[80–82].

JAK–STAT signalling. Constitutive activation of Janus kinase (JAK; also known as tyrosine protein kinase JAK)–signal transducer and activator of transcription (STAT) signalling in HRS cells is another major characteristic of cHL pathobiology. Whole-exome sequencing studies have shown high frequencies of mutations (in aggregate up to 90%) in the JAK–STAT pathways. In particular, inactivating *SOCS1* mutations and hotspot mutations in *STAT6* were reported in one study as the most frequent alterations (59% and 32% of patients, respectively)[57,83]. JAK–STAT pathway activation results in hyperphosphorylation of multiple STAT proteins (for example, STAT5A, STAT5B and STAT6) that transcriptionally regulate downstream targets[84,85]. In this context, the STAT3-mediated downstream target *BATF3* has been linked to *MYC* activation in cHL[86]. Besides the effect of these somatic mutations, constitutive activation of the JAK–STAT pathways is also enhanced by autocrine and paracrine signalling[87,88]. Overall, this documentation of JAK–STAT pathway activation strongly justifies therapeutic targeting with JAK inhibitors, which are currently being investigated in clinical trials[89,90].

Other aberrant signalling. In addition to JAK–STAT and NF-κB signalling, multiple additional signalling cascades have been found to be deregulated and constitutively activated in HRS cells[91]. This altered signalling includes activation of the phosphatidylinositol 3-kinase (PI3K)–RACα serine/threonine protein kinase (AKT) pathway by aberrant expression of multiple receptor tyrosine kinases, including platelet-derived growth factor receptor-α (PDGFRA), epithelial discoidin domain-containing receptor 2 (DDR2), high-affinity nerve growth factor receptor (also known as tyrosine kinase receptor A (TRKA)) and BDNF/NT-3 growth factor receptor (also known as TrkB tyrosine kinase (TRKB))[92]. These observations suggest that targeted treatment approaches using AKT pathway inhibitors as single agents or in combination to focus on the PI3K–AKT–mTOR pathway may prove quite effective[93]. Conversely, the demonstration of preclinical and clinical efficacy of mTOR inhibition in cHL demonstrates proof of concept for the importance of AKT signalling in cHL pathogenesis[94].

Tumour microenvironment biology in cHL

The cellular composition of cHL tumours includes only infrequent malignant cells surrounded by a particularly characteristic TME composed of a variety of non-cancerous immune and stromal cells, including several types of T cells, B cells, eosinophils, M1 and M2 macrophages and fibroblasts[74]. By contrast, specific histopathological characteristics separate NLPHL from cHL[1]. Of the cells present in the tumour, only approximately 1% are from the neoplastic clone (HRS cells in cHL and LP cells in NLPHL)[1]. The TME in cHL demonstrates a variable cellularity that is quite complex and different in each subtype of the disease (FIG. 4). One major distinguishing characteristic of the TME in NSHL is a dominant involvement of fibroblast-like cells and fibrosis. In MCHL, the TME consists of a polymorphous reactive infiltrate with B cells and T cells, neutrophils, eosinophilic granulocytes, macrophages, plasma cells and mast cells[95]. LDHL, a rare subtype of cHL, is related to MCHL and is characterized by relatively abundant HRS cells and macrophages, but only very few small lymphocytes, and has a TME usually composed of histiocytes with irregular fibrosis[96]. LRHL is equally rare and is rich in background non-malignant lymphocytes and B cells in particular, whereas the malignant HRS cells are characteristically increased in numbers in mantle and marginal zones of lymph node follicles[27]. In LRHL, the TME is variable but usually consists of histiocytes and lymphocytes. The TME of NLPHL is similar to that of LRHL, although in NLPHL it is also rich in follicular dendritic cells.

Evidence of extensive crosstalk between tumour cells and immune cells, mediated by a large network of cytokines and chemokines acting in an autocrine and paracrine manner, suggests that there is a pro-malignant 'cellular ecosystem' underlying cHL. The cellular composition of the TME in cHL, as well as the functional properties of the constituent non-neoplastic cells, further suggests the importance of this network[74]. The relative abundance of the cellular components (including HRS cells) in the TME can vary considerably between patients and the four histological subtypes of cHL. Sequencing and gene expression studies in HRS cells suggest that the genotype and phenotype of HRS cells strongly influence the cellular crosstalk within the TME. For example, genetic alterations (such as *B2M* mutations that lead to loss of expression of HLA class I molecules and, therefore, impair the ability of immune effector cells to recognize and interact with cells harbouring the mutations)

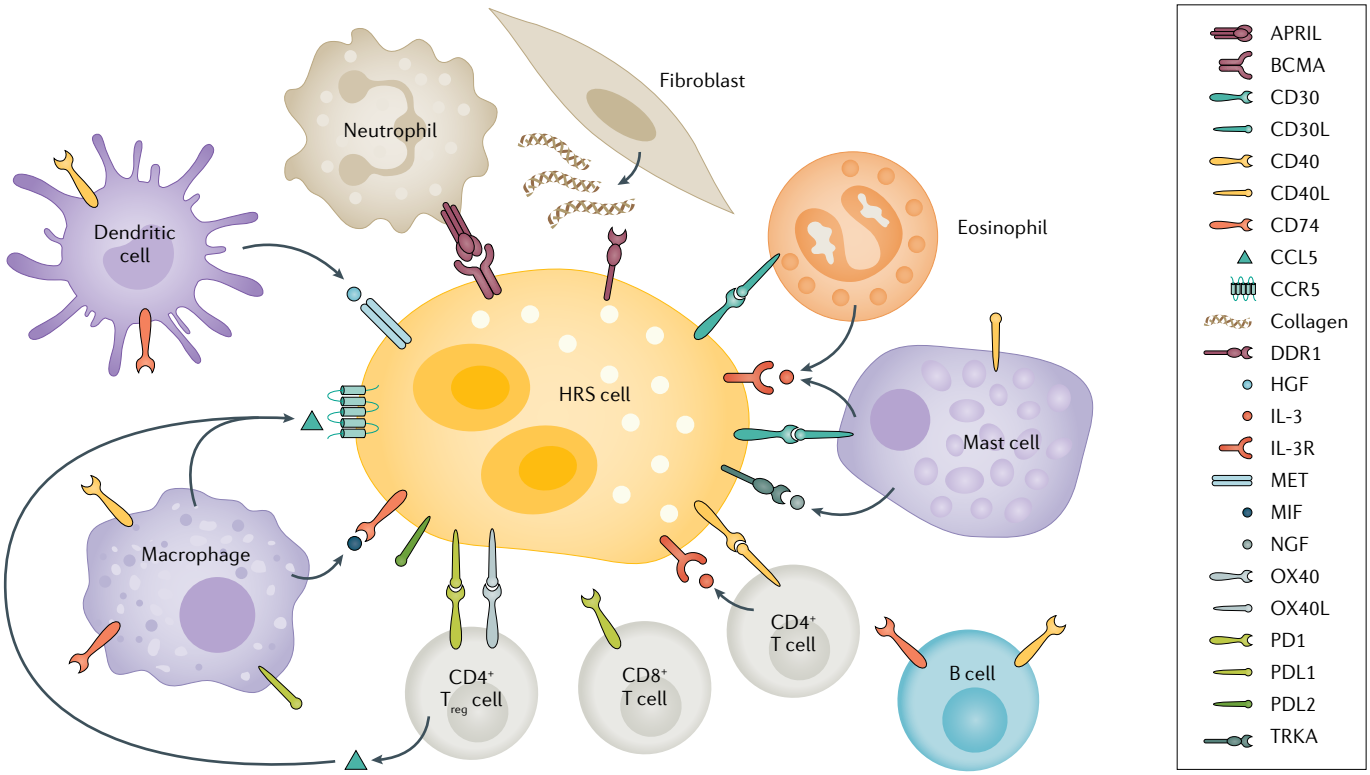

Fig. 4 | **Tumour microenvironment.** A diagnostic Hodgkin and Reed–Sternberg (HRS) cell surrounded by the inflammatory cellularity of the tumour microenvironment (TME), representative of the range of microenvironmental changes associated with all four types of classic Hodgkin lymphoma (cHL). The inflammatory cell infiltrate produces molecules that bind to proteins expressed on the cell membrane of the HRS cell. These interactions lead to activation of pathways that support the growth and survival of HRS cells. Independently of the cHL subtype, the reactive cells of the TME express and release molecules that have a crucial function in the growth and survival of tumour cells. Eosinophils and mast cells, which express CD30 ligand (CD30L), as well as neutrophils, which express a proliferation-inducing ligand (APRIL, also known as TNF ligand superfamily member 13), are commonly mixed with HRS cells. In addition, $CD4^+$ T lymphocytes, which express CD40 ligand (CD40L), surround HRS cells. These TME cells have a major role in immune evasion as they are capable of expressing PD1. Importantly, a subset of $CD4^+$ regulatory T (T_{reg}) cells (predominantly type 1 T helper (T_H1)-polarized) interact with HRS cells in concert with $CD4^+PD1^+$ T cells[74,95,102,264,265]. Overall, the non-neoplastic cells of the cHL TME interact with HRS cells in a complex ligand–receptor crosstalk[95,266]. BCMA, B cell maturation antigen; CD30L, CD30 ligand; CD40, CD40L receptor, also known as TNF receptor superfamily member 5; CD74, HLA class II histocompatibility antigen γ-chain; CCL5, CC-chemokine ligand 5; CCR5, CC-chemokine receptor 5; DDR1, discoidin domain receptor 1; HGF, hepatocyte growth factor; IL-3R, IL-3 receptor; MET, proto oncogene Met, also known as HGF receptor; MIF, migration inhibitory factor; NGF, nerve growth factor; OX40, OX40L receptor, also known as TNF receptor superfamily member 4; OX40L, OX40 ligand, also known as TNF ligand superfamily member 4; TRKA, tyrosine kinase receptor A.

differ substantially in frequency between the histological cHL subtypes and are encountered more frequently in NSHL, which is characterized by a prominent presence of fibroblasts[97] (FIG. 4). Moreover, evidence from gene expression profiling indicates that the composition of the TME varies according to the EBV tumour status[98]. In addition, findings from molecular epidemiology studies verify that host-specific variables that can modulate the TME have an important role in cHL pathogenesis, including overall host immune system function, patient age and specific genetic polymorphisms associated with immune responses[41,99,100].

T cells. Several TME alterations are common across the subtypes of cHL. HRS cells attract type 2 T helper (T_H2) cells, regulatory T (T_{reg}) cells and macrophages into the TME, and these cell types play a major part in maintaining an inflammatory microenvironment that supports malignant cell growth. There is evidence that factors that promote a T_H2 cell-dominated immune response are associated with an increased risk of cHL[23,101]. However, the widely accepted concept that the cHL TME is skewed towards a T_H2 cell-mediated immune response has recently been challenged by a study that, by using flow cytometry and extended immunohistochemistry[61], found a predominant T_H1 cell polarization. The presence of exhausted T cells (cells that have lost their effector functions following prolonged antigen exposure) and T_{reg} cells in the TME was confirmed using mass cytometry, and the same study also found that $CD4^+$ T_H1 cell-polarized T_{reg} cells and $PD1^+$ T_H1 cells are characteristic components of the T cell-rich cHL TME[63]. Very recently, a single-cell RNA sequencing study on 22 tissue samples defined the immune cell

composition of cHL at single-cell resolution and identified potentially targetable LAG3$^+$ T cells (expressing lymphocyte activation gene 3 protein (LAG3)) with immunosuppressive function as a key component of the TME[102]. These results highlight the need for more comprehensive characterization of the TME using multiparameter phenotyping.

Macrophages. Tumour-associated macrophages have been reported to be prominent myeloid lineage-derived cells that support HRS cell growth and participate in forming an immune-privileged niche. Importantly, the abundance of macrophages and an associated paucity of background non-malignant B cells are biomarkers predictive of treatment response for both primary treatment with ABVD (Adriamycin (a brand name for doxorubicin), bleomycin, vinblastine and dacarbazine)[58,98] and salvage therapy with ASCT[103]. A study of the extent of macrophage infiltration and expression of PD1 and PDL1 in the TME of cHL[62] found that PDL1 expression in the TME comes mostly from macrophages, and PDL1$^+$ macrophages (expressing PDL1) are more frequently localized near HRS cells than PDL1$^-$ macrophages. Moreover, PD1$^+$CD4$^+$ T cells were found to directly contact PDL1$^+$ macrophages and HRS cells more frequently than they contacted PDL1$^-$ macrophages, and PD1$^+$CD4$^+$ T cells were associated with PDL1$^+$ HRS cells more frequently than PD1$^+$CD8$^+$ T cells, highlighting the importance of the HLA class II–CD4$^+$ T cell axis in cHL pathogenesis. These findings fit well with previous results showing that HRS cells express HLA class II molecules more frequently than HLA class I molecules[104,105]. Furthermore, loss of expression of HLA class II molecules, which is known to be associated with poor treatment outcome, was found in ~40% of patients[104,106].

Somatically acquired immune privilege in cHL. The concept of 'acquired immune privilege', which postulates that HRS cells evade immune surveillance and shape a TME that favours their survival by acquisition of specific gene mutations (for example, in *CIITA*, *PDL1* (also known as *CD274*), *PDL2* (also known as *PDCD1LG2*), *PTPN1* and *B2M*, which encode proteins that are involved in immune cell recognition and regulation), is strongly supported by multiple genomics and TME studies[53,55,107,108]. HRS cells evade an effective immune response owing to genetic aberrations that alter TME interactions[53,109–111]. HRS cells often overexpress PDL1 and PDL2, encoded by genes located on chromosome 9p24.1, by increasing copy number (through gains and amplifications), as a consequence of EBV infection or chromosomal rearrangements[53,109–112]. The frequent occurrence of immune escape mediated by PDL1 alterations provides the rationale for the therapeutic use of PD1 blockade in cHL. The major antitumour mechanism of PD1 blockade in solid tumours is thought to be activation in the TME of CD8$^+$ cytotoxic T cells that recognize tumour peptides presented by HLA class I molecules[113–116]. However, effective antigen presentation by HRS cells is frequently disrupted by mutation-driven dysfunction or absence of the expression of HLA class I and II molecules, providing a strong biological rationale for testing HLA expression in the context of clinical decision making involving therapeutic PD1 blockade and alternative immune checkpoint inhibitors[55,102,105].

Tumour microenvironment biology in NLPHL

LP cells are found in follicular dendritic cell networks within tumour nodules that are composed of CD20$^+$ B cells and small IgD$^+$ B cells[28,117,118]. The tumour nodules resemble a primary lymphoid organ because they contain follicular dendritic cells admixed with reactive cells, including T cells[118]. Most LP cells are surrounded by T cells expressing CD3, CD4 and CD57 (REFS[28,117,118]). The CD4$^+$ T cells express PD1 and interferon regulatory factor 4 (IRF4; also called MUM1), consistent with these cells being a subset of germinal centre T cells[4,28,117,118]. The observation of CD4$^+$PD1$^+$ small T lymphocytes rosetting around typical CD20$^+$BCL-6$^+$ (expressing B cell lymphoma 6 protein (BCL-6)) LP cells is helpful for distinction of NLPHL from other conditions, including progressively transformed germinal centres, MCHL and T cell histiocyte-rich B cell lymphoma (TCRBCL). In addition, more recent studies have added substantial insight into the gene expression profiles and most frequent gene alterations in NLPHL. These studies have reinforced the previously suspected relatedness of NLPHL and TCRBCL phenotypes on the basis of gene expression profiling[45] and detection of common gene mutations of *JUNB*, *DUSP2*, *SGK1* and *SOCS1*, which are probably the products of aberrant somatic hypermutation in both entities[46].

Diagnosis, screening and prevention

Diagnostic evaluation, assignment of stage (which involves the use of sophisticated scanning techniques) and delivery of treatment for HL require commitment of extensive health-care resources, which, depending on the level of economic development of a region, may differ considerably around the globe (BOX 1). Recently, a group of international experts described resource-stratified guidelines for diagnosis and treatment, including those suitable for resource-constrained areas[119].

Classification of Hodgkin lymphoma

The diagnosis of HL has evolved substantially since the 1970s[1,120–124]. As described in the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues (revised fourth edition, 2017)[1], HL is distinguished into cHL and the less common NLPHL.

Classic HL. About 90% of all patients with HL have cHL[1], which is subdivided into four histological subtypes, based on the morphological characteristics of the tumour cells and the composition of the reactive immune cell infiltrate of the TME[1]. Among them, NSHL and MCHL are the most common forms[1].

More than 70% of patients with cHL have NSHL[1], and NSHL is histologically characterized by the presence of sclerosis, diagnostic HRS cells and other tumour cells with lacunar morphology. Lacunar cells, the characteristic HRS cells in NSHL, are large cells with abundant cytoplasm, lobated nuclei and small nucleoli. In formalin-fixed tissues, these cells appear retracted or

Box 1 | **Global variations in diagnosis, staging and management**

Diagnosis

Diagnostic evaluation of Hodgkin lymphoma is based on excisional biopsy of an entire involved lymph node. Using formalin-fixed paraffin-embedded tissue, the cellular morphology is determined with haematoxylin–eosin staining, and the phenotype of the neoplastic and background cells is determined using immunohistochemical staining for several markers. Essential markers to test for are CD3, CD15, CD20, CD30, CD45, paired box protein Pax-5, Epstein–Barr-encoding region (EBER) and Epstein–Barr latent membrane protein 1 (LMP1), and in special cases it is useful to test for CD21, CD57, CD79A, IgD, PD1, OCT2 and BOB1 Where resources are limited, as many markers as possible should be tested for, with priority given to CD15, CD20, CD30 and EBER.

Staging

Ideally, standard staging should consist of medical history; physical examination (with special attention to lymph node enlargement and abdominal organomegaly); complete blood cell counts; renal and liver function tests; tests for HIV, hepatitis B virus and hepatitis C virus infections; chest radiography; and PET–CT scan, which should be repeated after completion of treatment for assessment of response. Where resources are limited and PET scanning is unavailable, staging and treatment assessment should rely on CT scanning or, if CT is also unavailable, initial and repeat medical history, physical examination, chest radiography and laboratory tests. If PET scanning is unavailable, bone marrow biopsy should be added to complete staging.

Treatment

Treatment should include, as appropriate, chemotherapy and radiation therapy. Essential multidrug regimens are ABVD (Adriamycin (a brand name for doxorubicin), bleomycin, vinblastine and dacarbazine) or BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone). Where resources are limited, if ABVD chemotherapy is unavailable, less-expensive regimens such a ChlVPP (chlorambucil, vinblastine, procarbazine and prednisone) may be substituted. Essential radiation therapy includes external beam radiation delivered with a linear accelerator with treatment fields designed using CT-guided simulation and 3D treatment planning. Where resources are limited, if radiation treatment is unavailable, chemotherapy may be substituted.

shrunken and are located in a lacuna. In involved lymph nodes, there are groups of lacunar cells in a microenvironment containing inflammatory cells, including reactive T cells and B cells, granulocytes, histiocytes and fibroblast-like cells[95], surrounded by varying amounts of bands of collagen; for example, in the 'cellular phase' variant of NSHL, bands of collagen are absent, whereas in the 'total sclerosis' variant (FIG. 1), there is marked thickening of the nodule. In the 'syncytial variant' of NSHL, lacunar cells may form cellular islands that usually display central necrosis.

About 20–25% of patients with cHL have MCHL[1], and MCHL is more frequently encountered in patients with HIV infection and in resource-poor areas, possibly owing to its frequent association with EBV infection. It is characterized by diagnostic HRS cells in a mixed inflammatory TME without sclerosis. In comparison with the other types of cHL, pathognomonic binucleated and multinucleated HRS cells with huge nucleoli are present in greater numbers in MCHL. A mixed cellular microenvironment including reactive T cells and B cells, eosinophils, granulocytes, histiocytes, plasma cells and mast cells is a distinguishing characteristic of this subtype.

Only 3–5% of patients with cHL have LRHL[125,126]. LRHL morphologically resembles NLPHL, on the basis of its frequent nodular growth pattern and lymphocyte richness. However, phenotypically LRHL qualifies as cHL, with typical HRS cells, which are contained within nodules that are composed of numerous small lymphocytes. Although a subset of the HRS cells may morphologically resemble NLPHL tumour cells (LP cells), their immune phenotype is typical of classic HRS cells.

The least common subtype of cHL, LDHL[127], is rich in HRS cells, which reside within a TME depleted of non-neoplastic lymphocytes and characterized by diffuse fibrosis. A consistent feature of this subtype is the predominance of HRS cells within the TME.

NLPHL. NLPHL is a distinct type of HL with an indolent course that accounts for only 10% of all patients with HL[128]. NLPHL is a B cell lymphoma, as shown by its immune phenotype, and LP cells exhibit multilobated nuclei and multiple, inconspicuous, nucleoli[118]. On the basis of its histological, morphological and immunological features, NLPHL is further subdivided into six patterns[117]: classic nodular pattern; serpiginous, interconnected nodular pattern; nodular pattern with prominent extranodular LP cells; T cell-rich nodular pattern; diffuse pattern with a T cell-rich microenvironment; and diffuse, B cell-rich pattern. The first two patterns, also called 'typical histopathological patterns', have nodular growth with LP cells predominantly located within the nodules. The other patterns, also called 'histopathological variants', are associated with prominent extranodular LP cells and B cell depletion of the TME[129]. An additional nodular pattern in which LP cells are exclusively located within the nodules without invasion of the extranodular space has also been recognized[130,131]. Interestingly, a similar finding was noted in 61 of 206 patients with NLPHL studied in the European Task Force on Lymphoma Project[128]. In these patients, the LP cells were located solely within the nodular structures. On this basis, a new pattern called 'NLPHL in situ', or intrafollicular neoplasia, has been proposed[130,132,133]; however, this subtype has not been included in the latest version of the WHO classification of lymphomas[134] because its clinical implications have yet to be defined[135].

Changes in the revised 2017 WHO classification. Despite clarification and notation of additional phenotypic and molecular genetic characteristics, the overall classification of HL has remained substantially unmodified in recent years; however, changes regarding NLPHL and MCHL were introduced in the 2017 revised 4th edition of the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues[1]. Recent studies have indicated that NLPHL is a follicle-derived germinal centre B cell lymphoma[4,136], leading some authorities to suggest that it should be separated from HL and considered an indolent non-Hodgkin B cell lymphoma[136]. In fact, unlike HRS cells, LP cells lack CD30 and CD15 expression, are not associated with EBV infection and consistently express B cell-associated antigens. In addition, NLPHL may evolve morphologically and phenotypically into a 'TCRBCL-like transformation'[4], which behaves similarly to aggressive non-Hodgkin B cell lymphoma and should be treated with regimens appropriate for that type of neoplasm. Of note, LRHL has a morphology and phenotype that are intermediate between those of NLPHL and cHL[4]. The expression of CD30 and CD15 by tumour cells, which are also permissive

for EBV infection, helps to identify LRHL as a distinct subtype of cHL[137].

The 2017 revised classification introduced new subtypes of non-Hodgkin lymphoma that may complicate accurate diagnosis of cHL. It recognizes EBV$^+$ diffuse large B cell lymphoma, not otherwise specified. This new subtype is a diffuse large B cell lymphoma in which EBV$^+$ HRS cell-like tumour cells are observed; this lymphoma lacks an inflammatory infiltrate and sclerosis. EBV mucocutaneous ulcer (a provisional entity) was also introduced. These EBV-associated entities are included in the differential diagnosis of EBV-associated cHL. EBV infection of HRS cells is invariably present in immunodeficiency-associated cHL, mainly HIV-associated cHL, Hodgkin-type post-transplant lymphoproliferative disorder and iatrogenic immunosuppression-related lymphoma[33,77].

Diagnosis and staging

Patients with HL most commonly present with asymptomatic lymphadenopathy in the upper body, which is typically painless and slowly progressive. In the minority of patients who present with symptoms, these may be localized, resulting from compression of nearby structures (cough, chest pain, back pain and limitation of movement), or systemic (night sweats, unexplained weight loss and persistent or recurring fever). Uncommonly, HL may manifest as persistent, sometimes severe pruritus (itch) or localized pain induced by alcohol ingestion[138]. Investigation of symptomatic patients usually reveals enlarged lymph nodes either on physical examination or routine chest radiography or, occasionally, on abdominal CT scanning. Persistent otherwise unexplained lymph node enlargement, especially if associated with localized or systemic symptoms, should be investigated with excisional biopsy, which usually readily confirms the diagnosis. Blood tests may reveal anaemia, lymphopenia, leukocytosis or eosinophilia, but none of these findings is either dependable or diagnostic, and the majority of patients have normal or near normal blood cell counts. Confirmation of the diagnosis of HL by biopsy should be followed by standard staging, including complete physical examination, careful history searching for localized or systemic symptoms, chest radiography, whole-body CT and ^{18}F-fluorodeoxyglucose (FDG)-PET scanning, blood tests for liver and renal function and screening for underlying infection with HIV, hepatitis B virus or hepatitis C virus. Bone marrow biopsy and staging laparotomy, albeit previously quite useful for the accurate staging of HL, are no longer necessary when FDG-PET scanning is available[139]. Diagnostic and staging evaluation in regions where sophisticated histopathological assessment or CT or PET scanning are unavailable are discussed in BOX 1.

Lymph node biopsy. The excisional biopsy of potentially involved lymph nodes is the gold standard to establish the diagnosis of HL. Percutaneous core needle biopsy can be utilized as an alternative procedure when a lymphadenopathy or mass is recognizable in deep lymph nodes. However, a sufficiently large amount of tissue is required to enable morphological analysis and immunohistochemical staining[125]. The histological diagnosis of cHL depends on finding diagnostic HRS cells in the proper histological microenvironment[120,121] (FIG. 5). HRS cell variants, which include mononuclear variants, necrotic forms and lacunar cells, are useful for identifying histological cHL subtypes. However, in patients previously diagnosed with cHL, the presence of any variant of HRS cells is sufficient to confirm nodal or extranodal involvement of the disease, because in the large majority of patients the histological subtype is preserved even through multiple relapses. Difficulties in the histological diagnosis of HL may derive from the paucity of HRS cells (cHL) or LP cells (NLPHL) or the abundance of immune reactive and inflammatory cells and stromal changes.

HRS cells are almost invariably strongly positive for CD30 (REF.[140]), whereas expression of CD15 is variable but present in at least 75% to 85% of patients[1] (TABLE 2). Supportive evidence for cHL is provided by the expression of plasma cell markers (such as IRF4)[1,141] and of molecules involved in the presentation of antigens (CD40 ligand, T lymphocyte activation antigen CD80, T lymphocyte activation antigen CD86 and HLA class II molecules)[1], and the B cell-associated antigen paired box protein Pax-5 (PAX5) is expressed in almost all patients[1]. T cell markers (CD3), B cell markers (CD20, CD79A and CD79B)[142] and transcription factors (POU domain, class 2, transcription factor 2 (also known as OCT2), POU domain class 2-associating factor 1 (also known as BOB1) and transcription factor PU.1)[50,143] and germinal centre B cell markers (BCL-6 and AID) are generally not expressed by HRS cells[125], documenting the unique phenotype of HRS cells. HRS cells also often express PDL1, PDL2, NOTCH1, CAMPATH1 antigen (also known as CD52) and histone deacetylase 6 (HDAC6), which are potential targets for therapy[144,145]. The expression of the majority of these markers is heterogeneous in the different cHL subtypes.

EBV tumour status. As discussed in the Epidemiology section, the prevalence of EBV in HRS cells (EBV tumour status) varies considerably across the cHL subtypes. When available, testing for the presence of EBV in HRS cells should be included in the diagnostic evaluation, as it provides information that helps determine the histological subtype. For example, EBV infection can be documented in ~75% of patients with MCHL and LDHL[3], whereas NSHL and LRHL are less frequently associated with EBV. EBV infection can be detected in HRS cells through in situ hybridization of EBV-encoded RNA (FIG. 5). This evidence, in addition to the expression of the viral oncoprotein LMP1, which activates signalling pathways promoting survival of precursor tumour cells in EBV-associated cHL[76,77], is suggestive of a pathogenetic role of EBV in HL in a number of patients[77].

Staging. The Cotswold modification of the original Ann Arbor staging system added a measure of tumour bulkiness to the stage based on the extent of lymph node and extranodal disease[146] (BOX 2). For purposes of planning treatment, two approaches to subdividing patients into staging subgroups have emerged, one in which

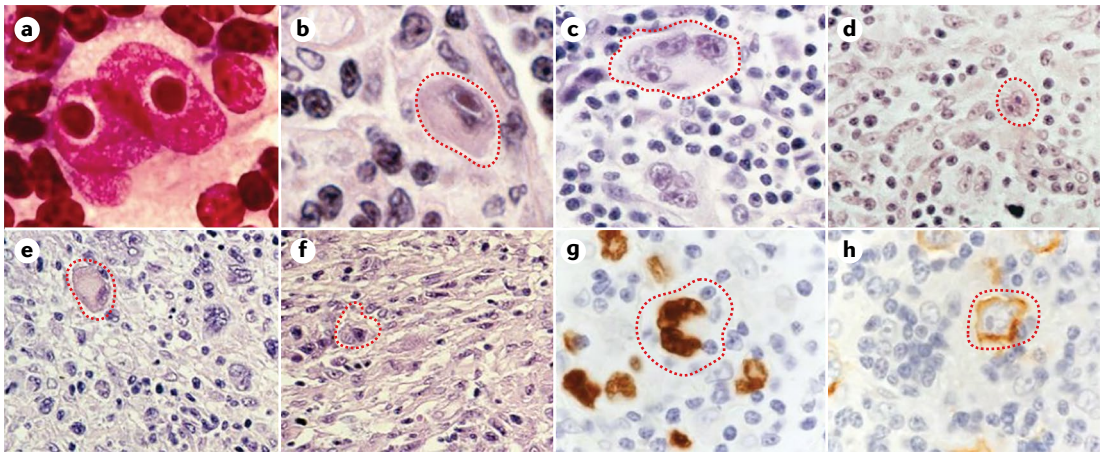

Fig. 5 | **Morphological features of HRS cells and EBV infection of HRS cells.** Hodgkin and Reed–Sternberg (HRS) tumour cells of classic Hodgkin lymphoma (cHL) are morphologically characterized by extensive eosinophilic cytoplasm and typically two multilobated nuclei (Reed–Sternberg cells), with huge, round, inclusion-like nucleoli. Binuclear cells have an 'owl's eye' appearance due to a perinucleolar halo (part **a**, original magnification ×100). The mononuclear variant of HRS cells (termed a Hodgkin cell) is a giant cell with a prominent nucleolus and is usually found in mixed cellularity HL (part **b**, original magnification ×60). Necrotic forms, also referred to as 'mummified' cells, are cells with pyknotic (with condensed chromatin) nuclei and eosinophilic cytoplasm that are commonly encountered in biopsy sections from cHL (not shown). Lacunar cells have the appearance of large multilobated cells with inconspicuous nucleoli and abundant cytoplasm and are found in tissue spaces (or lacunae), an artefact that arises owing to cytoplasmic contraction during formalin fixation. These lacunar cells are subtype-specific forms of HRS cells found in nodular sclerosis HL (part **c**, original magnification ×40; part **d**, original magnification ×20). In lymphocyte-depleted HL, the HRS cells are pleomorphic with a sarcomatous appearance (similar to cancerous connective tissue cells) and may resemble the anaplastic (poorly differentiated) tumour cells observed in non-Hodgkin lymphomas (part **e**, original magnification ×40; part **f**, original magnification ×20). Epstein–Barr virus (EBV) infection of HRS cells can be demonstrated by Epstein–Barr-encoding region (EBER) in situ hybridization (which detects EBV-encoded RNA) (part **g**, original magnification ×60) and immunohistochemical staining to detect latent membrane protein 1 (LMP1) expression, which is cytoplasmic and membranous (part **h**, original magnification ×40). Touch imprint cytology slide stained with haematoxylin and phloxin (part **a**). Formalin-fixed paraffin-embedded tissue sections stained with haematoxylin and eosin (parts **b**–**f**). Formalin-fixed paraffin-embedded tissue sections (parts **g** and **h**).

patients are divided into two subgroups, with limited-stage or advanced-stage disease, and another in which patients with limited-stage disease are further subdivided into two groups. In the two-stage system, often employed in North America, ~30% of patients present with limited-stage disease (stage I or II disease with no B symptoms and absence of bulky disease or stage IB disease without bulky disease), and the other 70% of patients present with more advanced disease (stage II disease with B symptoms or bulky disease, or stage III or stage IV disease)[147], where bulky disease is defined as a tumour diameter of ≥10 cm or a mediastinal mass ratio (MMR; that is, the maximum width of the largest mediastinal mass divided by the maximum intrathoracic diameter, as measured on chest radiography) of >0.33.

In the three-stage approach, often employed in Europe, the designation of advanced stage is reserved for the ~50 % of patients with Ann Arbor stage III or IV, and the other 50% of patients are classified as having favourable (~25%) or unfavourable (~25%) limited-stage (stage I or stage II) disease, on the basis of absence (favourable) or presence (unfavourable) of specific risk factors. These risk factors differ slightly in different organizations. The German Hodgkin Study Group considers the following as risk factors: an erythrocyte sedimentation rate (ESR; which indicates the presence of inflammation if higher than normal) >50 mm per hour with no B symptoms; ESR >30 mm per hour with B symptoms; MMR >0.33; more than two involved lymph node sites; and the presence of any extralymphatic lesion[148]. The European Organisation for Research and Treatment of Cancer (EORTC) considers the following as risk factors: age ≥50 years; ESR >50 mm per hour with no B symptoms; ESR >30 mm per hour with B symptoms; a mediastinal thoracic ratio >0.35; and more than three involved lymph node sites[149]. Finally, the National Comprehensive Cancer Network considers the following as risk factors: ESR ≥50 mm per hour; B symptoms; MMR >0.33; more than three involved lymph nodes sites; and the largest tumour diameter >10 cm (REF.[150]).

Screening and prevention

Screening and prevention procedures for HL are not feasible at present. HL is too rare, and no tests with sufficient sensitivity and specificity to justify post-test intervention have been identified or shown to be effective. Even in the case of patients with HL with an identical twin, who has a very high relative risk and a finite window of time through young adulthood during which the risk of HL occurrence is highest[100], no practical screening methods have been identified. Several other populations with modestly higher than average risk of developing HL have been identified, but, again, no practical screening method

Table 2 | **Molecular characteristics of Hodgkin lymphoma**

Biomarker	NSHL	MCHL	LDHL	LRHL	NLPHL
CD30	Positive	Positive	Positive	Positive	Negative
CD15	Usually positive (~80%)	Usually positive (~80%)	Usually positive (~80%)	Usually positive (~80%)	Negative
IRF4	Positive	Positive	Positive	Positive	Positive
CD20	Occasionally positive (~20%) with variable intensity	Occasionally positive (~20%) with variable intensity	Occasionally positive (~20%) with variable intensity	Occasionally positive (~20%) with variable intensity	Positive
PAX5	Positive	Positive	Positive	Positive	Positive
B cell transcription factors	Usually negative	Usually negative	Usually negative	Positive or negative	Positive
EBV	Positive (10–20%)	Positive (75%)	Positive (75%)	Positive (30%)	Negative

Based on REF.[1]. EBV, Epstein–Barr virus; IRF4, interferon regulatory factor 4; LDHL, lymphocyte-depleted Hodgkin lymphoma; LRHL, lymphocyte-rich Hodgkin lymphoma; MCHL, mixed cellularity Hodgkin lymphoma; NLPHL, nodular lymphocyte-predominant Hodgkin lymphoma; NSHL, nodular sclerosis Hodgkin lymphoma; PAX5, paired box protein Pax-5.

has emerged. These groups include young adults in the 5-year period following infectious mononucleosis (on the basis of a prospective study in Denmark[25]), siblings and twins of patients[151], and HIV-positive individuals[152]. Case–control studies have analysed associations between obesity[153] and a dietary inflammatory index (which assesses the likelihood that specific nutrients induce inflammatory cytokines)[154] and the risk of HL[155], but these studies could not be duplicated and, therefore, are not definitive. Development of an EBV vaccine that could prevent the fraction of cHL cases caused by this virus (estimated at 1 case per 1,000 at-risk individuals)[25] is ongoing, but there is no licensed vaccine yet[156].

Management

The overall goal of treatment for HL is to cure the disease while exposing the patient to the least acute or, in particular, long-term toxicity. To achieve this result, several factors are taken into consideration: the subtype of HL (either cHL, including cHL that cannot be further subtyped (FIG. 6), or NLPHL (FIG. 7)); the stage and stage subgroup of the disease; and the patient's degree of frailty, which reflects both age and comorbid medical conditions such as diabetes mellitus, cardiac disease or other organ dysfunction. Across the field of oncology, HL stands out as one of the diagnostic entities for which the choice of primary and secondary treatment has been most consistently based on prospective clinical trials. Interpretation of these trials requires careful definition of end points to assess the quality of the treatment response and interpretation of the results of functional imaging techniques and survival outcomes. Definitions of the terms typically employed for the interpretation of clinical trials are provided in BOX 3.

Prognosis

Through the 1940s, HL was nearly uniformly fatal. Today, the standard expectation is cure, which makes HL treatment a remarkable success story. Combined-modality treatment regimens composed of multiagent chemotherapy, meticulously planned radiation and, more recently, immunotherapy were often first demonstrated to be effective in HL and are now routine across oncology. Striking a balance between improved effectiveness, often achieved with high-intensity treatment, and late-onset treatment-related complications, such as heart disease and second neoplasms, has proven challenging and is only achievable through careful analysis of long-term monitoring. Most clinicians outside Europe have adopted a practical therapeutic approach in which patients are considered to have either limited-stage or advanced-stage disease (two-stage approach), whereas clinicians in Europe usually adopt a three-stage approach, in which patients have favourable or unfavourable limited-stage disease (depending on the presence or absence various risk factors) or advanced-stage disease. Cure rates are 90–95% for nonbulky stage IA or stage IIA disease and 70–80% for advanced-stage disease[5–7,10,11,157–159]. Prognostic models such as the International Prognostic Factors Project score (IPS), which is based on the number of independent predictors of progression (age, sex, disease stage, haemoglobin level, white blood cell count, lymphocyte count and serum albumin level), provide validated estimates of probable progression-free survival (PFS) and overall survival (OS) in patients with advanced-stage disease[30]. When first developed in the 1980s to reflect outcomes of treatment with ABVD, the IPS predicted that patients with no risk factors had a 5-year freedom from progression (FFP) of 84%, but those with all seven factors had a 5-year FFP of 42%, a spread of 42%. However, over time, the use of improved imaging techniques has resulted in more precise staging, as some patients who were formerly considered to have limited-stage disease are now considered to have advanced-stage disease, more accurate diagnosis has enabled removal from analyses of those patients who actually have non-Hodgkin lymphoma, and clinicians have learned to pay more careful attention to full dose delivery. Reflecting these changes, current outcomes achieved using the same ABVD chemotherapy show a spread of only 17% between the best and worst groups, with all IPS subgroups experiencing improved outcomes[160] (FIG. 8). Overall, at least 90% of patients in the age range 16–70 years can anticipate being cured, if not with primary treatment then with effective secondary interventions.

Treatment of limited stage HL

The most commonly employed approaches to the treatment of limited-stage cHL in both North America and Europe include an initial phase of chemotherapy followed by a consolidation phase consisting of radiation therapy[149,150] (FIG. 6). When treatment is based on a two-stage system, the most commonly chosen approach comprises brief chemotherapy, typically two to three cycles, followed by radiation therapy[150]. When treatment is based on a three-stage system, often referred to as risk-stratified treatment, this same approach is usually recommended in patients with favourable limited-stage disease, but in patients with unfavourable limited-stage disease prolonged chemotherapy, typically four cycles, is employed before the consolidation radiation therapy[149]. Guidelines for the treatment of limited-stage NLPHL in North America and Europe generally match those for cHL, with the exception that patients with quite localized disease (stage IA) may be treated with radiation alone[149,150] (FIG. 7).

Until the early 2000s, patients with limited-stage disease typically received chemotherapy to eradicate subclinical systemic disease and wide-field radiation therapy to cure the disease in the presenting sites and nearby lymph node regions. However, patients treated in clinical trials from the 1960s to the 1990s were found to have long-term excess mortality from cardiovascular disease and second neoplasms, reflecting local organ toxicity due to the use of wide-field radiation therapy[161]. Much of this radiation-related toxicity can be eliminated (without a reduction in treatment effectiveness) by reducing the radiation field size to the involved site or, more recently, the involved lymph node, or reducing the radiation dose from the previously recommended 35–40 Gy to 20 Gy (REFS[162–165]). Even with a reduced field size or radiation dose, a concern for radiation-related toxicity arises when the treatment fields include substantial exposure of the breasts in young women or the heart, a risk that can be minimized with modern radiation therapy techniques. Important innovations in radiation therapy delivery (such as intensity-modulated radiation therapy, volumetric modulated arc therapy, treatment delivery during deep inspiration breath-hold, and image-guided radiation therapy) can further reduce unintended irradiation of organs at risk[166–168]. More recently, proton therapy, which uses a beam of protons instead of electrons as the source of ionizing radiation to treat diseased tissue, has been introduced for the management of mediastinal HL, bringing more -precise delivery of the radiation to the tumour tissue and dosimetric advantages that further reduce the dose delivered to organs at risk[169].

Therapy regimens. Extensive experience from clinical trials and case series from individual treatment centres shows that a brief course (typically two or three cycles) of chemotherapy with ABVD followed by involved-field radiation therapy cures ~95% of patients with limited-stage disease[5,6,165,170,171]. This approach also nearly completely eliminates the risks of infertility, premature menopause and leukaemia and minimizes cardiopulmonary toxicity while maintaining treatment effectiveness[165]. A 2012 randomized trial that compared four to six cycles of ABVD chemotherapy alone with wide-field (and now outmoded) radiation therapy, either alone or augmented with two cycles of ABVD chemotherapy, demonstrated that OS with chemotherapy alone was at least equivalent to that with radiation therapy-based treatment. However, the radiation-based approach led to a modest improvement in PFS[7]. At 12 years of follow-up, ABVD therapy alone was associated with an OS of 94%, establishing a useful benchmark for future trials[7]. More recently, this observation has led to trials in which a good initial response to treatment, usually documented on PET imaging, is used to justify stopping radiation therapy in these patients, potentially eliminating the risks associated with exposure to radiation, although with an increased risk of relapse of ~5%[5,6,170].

These observations provide evidence that individual patients can be treated with chemotherapy either alone, which minimizes potential cardiac and pulmonary toxicity, or together with radiation, which reduces primary treatment failures. Alternatively, on the basis of a good early treatment response documented on PET imaging, treatment may be limited to chemotherapy alone to completely avoid the use of radiation. Primarily in Europe, high-intensity approaches to the treatment of unfavourable limited-stage HL with adverse prognostic factors have been tested. Two cycles of bleomycin, etoposide, doxorubicin (Adriamycin), cyclophosphamide, vincristine, procarbazine and prednisone (BEACOPP) followed by two cycles of ABVD before involved-field radiation therapy significantly improved tumour control compared with four cycles of ABVD before involved-field radiation therapy, but OS did not improve, and the

Box 2 | **Cotswold modification of the original Ann Arbor staging system for Hodgkin lymphoma**

Stages

Stage I: Single lymph node region (I) or single local extralymphatic site (IE)
Stage II: Two or more lymph node regions on the same side of the diaphragm (II) or one or more lymph node regions with local extralymphatic extension, all on the same side of the diaphragm (IIE)
Stage III: Lymph node regions on both sides of the diaphragm (III), which may be accompanied by local extralymphatic extension (IIIE)
Stage IV: Diffuse involvement of one or more extralymphatic organs or sites

Additional variables

A: Free from the presence of B symptoms (persistent otherwise unexplained fever, night sweats or weight loss of >10% of body weight over 6 months)
B: Presence of any B symptoms
X: Bulky nodal disease: mediastinal nodal mass of one-third or more of the intrathoracic diameter or ≥10 cm in diameter

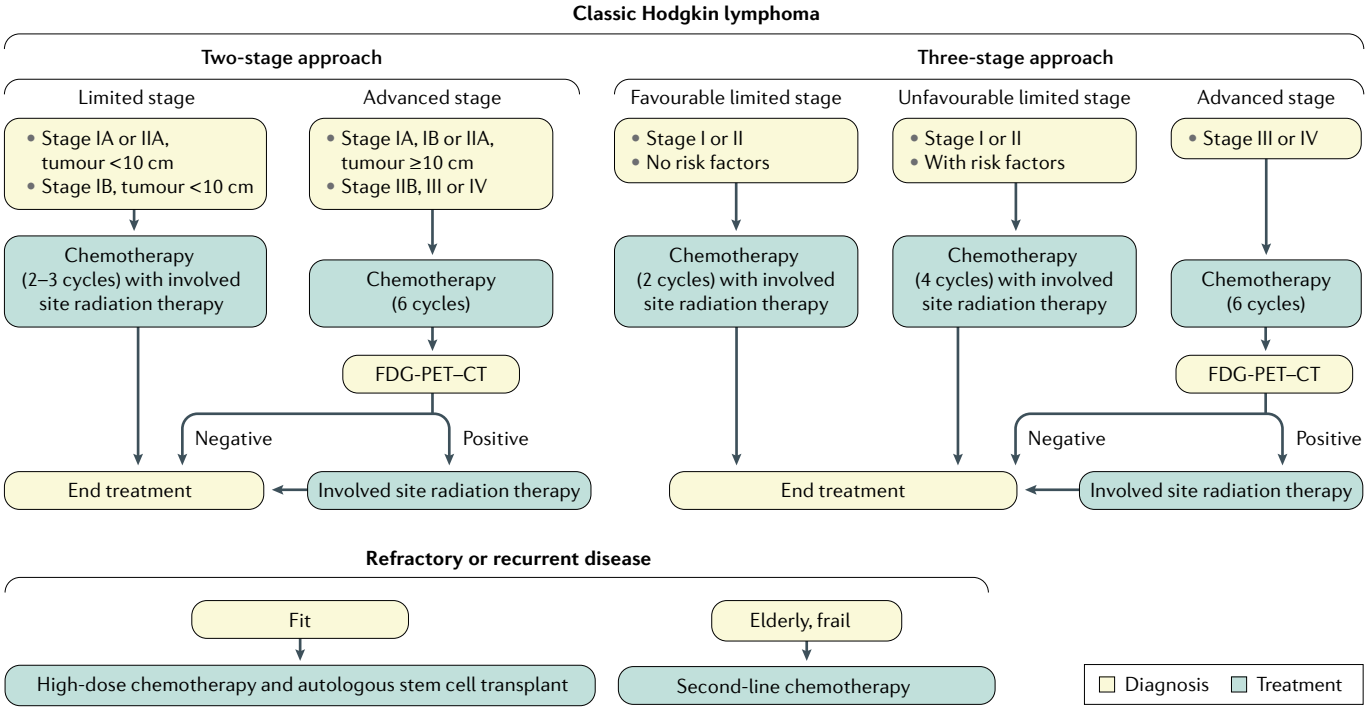

Fig. 6 | **Management algorithm for classic Hodgkin lymphoma.** Flow charts for the standard management of classic Hodgkin lymphoma. The subtype and stage of the disease determine the course of action, and the patient's characteristics (for example, age, overall health and comorbid conditions) should also be considered when planning the therapy. In some centres the patients are classified as having limited-stage or advanced-stage disease (two-stage approach), and in others as having favourable limited-stage, unfavourable limited-stage or advanced-stage disease (three-stage approach). FDG, ^{18}F-fluorodeoxyglucose.

toxicity was much greater with the BEACOPP approach than with the ABVD and radiation therapy approach[157].

Treatment of advanced-stage HL

The most commonly employed approach to the management of advanced-stage disease in both cHL and NLPHL throughout North America and Europe consists of at least six cycles of multiagent chemotherapy[149,150] (FIGS 6,7). Recently, in single-centre studies, managing advanced-stage NLPHL similarly to advanced-stage indolent non-Hodgkin lymphoma, that is, deferring treatment in asymptomatic patients (so-called watch-and-wait approach)[172] and treating symptomatic patients with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP)[173], resulted in outcomes similar to those observed following more conventional treatment. If these results can be duplicated at other centres, these watch-and-wait and R-CHOP approaches may be reasonable alternatives in patients with advanced-stage NLPHL. In patients with cHL, although ABVD has become the most widely used regimen internationally, BEACOPP is considered the standard in much of central and northern Europe. Although addition of radiation therapy significantly improves PFS at 10 years in patients with advanced-stage HL, it does not improve OS[158], leading many authorities to conclude that the adverse long-term effects of radiation therapy seem to outweigh any benefits in the typical patient with advanced-stage disease and, therefore, patients who achieve a complete response after primary chemotherapy do not require radiation, even when bulky disease was present at diagnosis. Functional imaging can provide useful guidance in this situation. Patients who, at the end of primary chemotherapy, harbour a persistent mass (documented on CT scan) at a site of initial involvement, including those with initially bulky disease (usually defined as a tumour mass of >10 cm in maximum diameter), can be assessed with FDG-PET. This technique distinguishes between residual fibrosis (negative PET scan, with no FDG signal (that is, no FDG uptake by tumour cells)) and persistent lymphoma (positive PET scan) and identifies the ~75% of patients whose residual mass is due to fibrosis and, therefore, do not require radiation therapy[10]. For the 25% of patients with a PET-positive residual mass, radiation therapy seems prudent, especially now in an era with refined dosimetry and precise delimitation of field size.

Treatment regimens. Although there have been several attempts to improve on the results with ABVD in patients with advanced-stage HL, such as the Stanford V (doxorubicin, vinblastine, mechlorethamine, etoposide, vincristine, bleomycin and prednisone) regimen[11,159], only escalated BEACOPP remains as a valid option (TABLE 3). Assessment of the effectiveness of primary treatment of advanced-stage HL with escalated BEACOPP compared with ABVD requires consideration of potential secondary treatments in those not cured by primary therapy. Thus, although escalated BEACOPP offers better initial disease control than ABVD, randomized

trials have failed to demonstrate superior OS, primarily because secondary high-dose chemotherapy followed by ASCT can rescue about 50% of the patients not cured by primary treatment with ABVD[15,16,174–178]. An alternative approach to improving on the results of treatment with ABVD by reducing toxicity was examined in the RATHL (Response Adapted Treatment of HL) trial, which demonstrated that bleomycin could be removed from further treatment, if an interim FDG-PET scan was negative, while maintaining the effectiveness of the chemotherapy[179].

Treatment based on functional imaging. The wide availability of functional imaging with FDG-PET has led to attempts to improve treatment outcomes in HL by integration of this new imaging technique. Such PET-driven approaches have been applied to both limited-stage and advanced-stage management. Measuring the response by FDG-PET after initial brief chemotherapy may identify patients with a response of sufficiently high quality to permit omission of radiation therapy[5,6,170], albeit at the risk of a modestly increased risk of relapse. This observation provides patients and clinicians with the opportunity to personalize treatment by choosing either to maximize the likelihood of initial disease control by including radiation therapy when the risks associated with radiation are considered minimal or to avoid radiation when its risks are considered potentially unwarranted.

Two opportunities to improve treatment outcome have emerged from the application of FDG-PET-driven management choices for advanced-stage HL. The first is provided by the ability of FDG-PET imaging to accurately distinguish between fibronecrotic debris and active lymphoma in residual masses detected radiologically at the end of primary chemotherapy, and this approach is now widely applied. The other opportunity is the use of interim FDG-PET scanning, typically after two cycles of chemotherapy, to guide further treatment of advanced-stage HL, but this approach has proven more controversial. On the one hand, in patients being initially treated with ABVD, a negative interim FDG-PET scan can enable removal of bleomycin from further cycles, thereby avoiding further bleomycin-associated pulmonary toxicity[179]. On the other hand, a positive interim FDG-PET scan might justify escalation to stronger but more toxic chemotherapy, such as escalated BEACOPP[12,179–181]. For patients being initially treated with intensive chemotherapy such as escalated BEACOPP, a negative interim FDG-PET scan can justify de-escalation of the chemotherapy to a regimen such as ABVD[13] or a shorter course of intensive chemotherapy[14].

The use of interim FDG-PET to escalate or de-escalate the intensiveness of further treatment remains controversial for several reasons. First, it improves on previous standard management primarily by reducing toxicity, but it does not improve overall outcomes in all treated patients. Second, there is no consensus on the definition of positive interim FDG-PET scan, with various conflicting proposals still being evaluated[13,182]. Third, the applicability of interim FDG-PET scan results when novel agents are added to primary chemotherapy is unproven, with some results indicating that adding novel agents eliminates the prognostic impact of interim FDG-PET scan results[65,183].

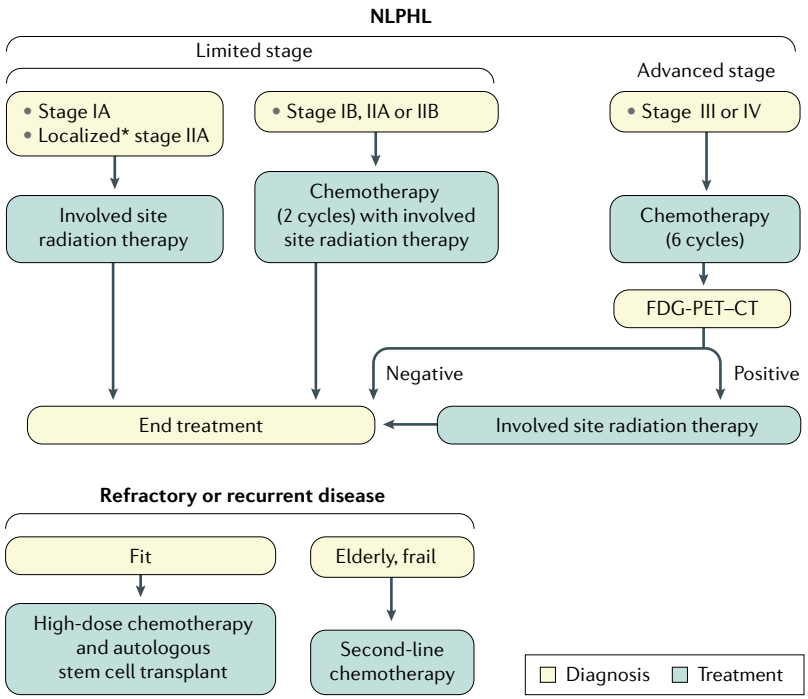

Fig. 7 | **Management algorithm for nodular lymphocyte-predominant Hodgkin lymphoma.** Flow chart for the standard management of nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL). Asterisk, 'Localized' indicates two closely contiguous nodal sites. FDG, ^{18}F-fluorodeoxyglucose.

New agents. Another way to improve outcomes in patients with HL, especially those with advanced-stage disease, is to incorporate new agents with novel mechanisms of action but with at most minimal overlapping toxicity into primary treatment. Brentuximab vedotin is an antibody–drug conjugate composed of a monoclonal antibody to the CD30 antigen universally expressed by malignant HRS cells (brentuximab) linked with several molecules of monomethyl aurostatin E (MMAE), a potent microtubule disrupter (vedotin). Brentuximab vedotin binds to surface CD30 and then is internalized into the cell. Lysozymes digest the protein antibody and the linker joining it to the MMAE, which then disrupts internal cellular structures and triggers apoptosis. As a single agent, brentuximab vedotin induced an overall response rate of 75% and a complete response rate of 34% in a phase II study enrolling patients with HL who had relapsed after prior treatment with ABVD and high-dose chemotherapy followed by ASCT[184]. Of the complete responders, ~30% maintained the complete response for >5 years without any further treatment and were considered to have probably been cured[185]. Consolidation brentuximab vedotin following ASCT reduced the probability of relapse after ASCT by ~30% in the AETHERA trial from ~60% to <40%[186,187]. Altogether these findings demonstrate that brentuximab vedotin can cure HL that had not been cured by either standard dose or intensified dose chemotherapy.

Box 3 | **Clinical trial end points used to assess response to treatment and outcomes in Hodgkin lymphoma**

Complete metabolic response (CMR): Deauville criteria (D) D1 or D2 response during treatment (interim response) and D1, D2 or D3 response at the end of treatment. CMR at the end of treatment is considered a complete response even in the presence of a residual mass on the CT scan.

Complete response (CR): all evidence of persistent Hodgkin lymphoma has resolved.

Deauville criteria (D): specific criteria used to quantify the uptake of radiolabelled ^{18}F-fluorodeoxyglucose (FDG) by the tumour and thereby assess the degree of response to treatment on the basis of FDG-PET scanning. D1, no uptake; D2, uptake ≤ uptake in the mediastinal blood pool; D3, uptake > uptake in the mediastinal blood pool but ≤ uptake in the liver; D4, uptake > uptake in the liver; D5 uptake markedly increased from baseline or in new lesions.

Overall response rate (ORR): total percentage of patients with CR or partial response; of note, ORR includes patients with a clearly measurable reduction in aggregate (total) tumour mass.

Overall survival (OS): time from diagnosis or initiation of planned treatment to the observed date of death from any cause (event) or the most recent date on which the patient remained alive. In a Kaplan–Meier estimation, death is considered an event, leading to a decrement in the survival estimation. If death has not occurred (no event), that patient's survival is censored (noted without a decrement in the survival estimation) on the date the patient was last observed alive. The OS assesses the overall effect of all treatments, primary and subsequent.

Partial response (PR): measurable sites of disease persist but have regressed by >50% in area (product of the two longest perpendicular diameters on the CT scan).

Progression: increase in the size of measurable lesions or appearance of a new lesion on the CT scan. Increase in size is defined as >50% increase in the sum of the products of the longest perpendicular diameters of up to six representative nodal or extranodal lesions or as the appearance of new lesions.

Progression-free survival (PFS; sometimes referred to as freedom from treatment failure (FFTF) or failure-free survival (FFS)): time from diagnosis or initiation of planned treatment to the date the individual last had no evidence of progression (censored observation using Kaplan–Meier estimation) or the actual date that progression was observed or death from any cause occurred (events). PFS assesses the effectiveness of the primary treatment and is often accepted as proof of superiority of primary treatment even in the absence of a difference in OS, because OS reflects the cumulative effect of primary and all subsequent treatments.

Time to progression (TTP; also referred to as freedom from progression (FFP)): time from diagnosis or initiation of planned treatment to the date the individual last had no evidence of progression or died without evidence of disease (censored observation using Kaplan–Meier estimation), or the date on which progression occurred or death related to treatment occurred (events). TTP assesses the effectiveness of primary treatment without the confounder introduced by causes of death unrelated to Hodgkin lymphoma or toxicity of treatment, which is included when PFS is used.

Recently, the ECHELON-1 trial (NCT01712490) compared standard ABVD with doxorubicin, vinblastine and dacarbazine (AVD) and brentuximab vedotin in 1,334 patients with stage III or IV HL[65,183], and the AVD and brentuximab vedotin combination resulted in a superior 3-year PFS of 83% compared with the 76% observed in those treated with standard ABVD[183]. In other words, 24% and 17% of patients in the ABVD arm and the AVD and brentuximab vedotin arm, respectively, relapsed within 3 years, that is, 7% fewer relapses occurred in the AVD and brentuximab vedotin arm. These findings imply that ~29% (7/24) of the patients who would have relapsed after treatment with ABVD did not relapse after treatment with the novel AVD and brentuximab vedotin combination[65]. Although moderate additional toxicity, consisting of mostly reversible peripheral nerve toxicity (89% of patients treated with AVD and brentuximab vedotin either had no peripheral nerve toxicity or resolution to an asymptomatic state) and more frequent neutropenia, resulted from adding brentuximab vedotin to AVD, these toxicities could be successfully managed by appropriate dose modifications and the use of a neutrophil growth factor. Additionally, complete elimination of bleomycin reduced the risk of pulmonary toxicity. Of note, interim FDG-PET scanning was not used to guide treatment in the ECHELON-1 trial. Whether interim FDG-PET scanning could usefully guide primary chemotherapy with AVD and brentuximab vedotin remains unknown.

Follow-up after primary treatment

The majority of patients with both limited-stage and advanced-stage HL reach a complete remission of their disease by the end of planned treatment. These patients initially should have a check-up visit every 3 months for the first 2 years of follow-up, then, at increasingly longer intervals up to annually after 4 to 5 years from completion of treatment[149,150]. At these follow-up visits, patients should undergo physical examination and blood tests to determine peripheral blood counts and liver and renal function. Persistent new, otherwise unexplained, symptoms such as fever, weight loss, night sweats, cough or localized masses or pain should be investigated to rule out recurrence; however, routine surveillance with CT or PET scans of asymptomatic patients has not proven useful and should be avoided.

Treatment of refractory or recurrent HL

The established treatment for patients whose HL persists or recurs despite primary therapy (that is, refractory or recurrent HL) is usually high-dose chemotherapy followed by ASCT[15,16,188]. However, the benefit of ASCT is offset by treatment-related mortality, frequent induction of infertility and increased risk of second neoplasms. These toxicities, the high cost of ASCT and the lack of evidence that ASCT improves OS if incorporated into primary treatment indicate that ASCT is best reserved for patients whose disease progresses despite optimal primary therapy. Major factors to be considered when ASCT is planned include the possibility of

adding a second-line chemotherapy regimen before the high-dose chemotherapy regimen; the choice of the high-dose chemotherapy regimen itself; the source of haematopoietic stem cells; the expected ASCT-related mortality; and long-term toxicity including induction of second neoplasms[188]. A variety of second-line chemotherapy regimens have been used in the past, but none has emerged as clearly superior; these include most commonly: ifosfamide, carboplatin and etoposide (ICE)[189]; dexamethasone, cytarabine and cisplatin (DHAP)[190]; gemcitabine, dexamethasone and cisplatin (GDP)[191]; and gemcitabine, vinorelbine and liposomal doxorubicin (GVD)[192]. Currently, novel agents such as brentuximab vedotin and the immune checkpoint inhibitors are being tested in this role either as single agents or, more usually, in combination with traditional agents, but again none has emerged as clearly superior. Similarly, a variety of high-dose chemotherapy regimens have been used before ASCT, but yet again none has emerged as clearly superior; these include: carmustine, etoposide, cytarabine and melphalan (BEAM)[16]; cyclophosphamide, carmustine and etoposide (CBV)[193]; and high-dose etoposide and melphalan[194]. High-dose chemotherapy regimens that include whole-body radiation therapy have been abandoned owing to unacceptably high rates of second neoplasms. Haematopoietic stem cells gathered from peripheral blood by apheresis have become the stem cells of choice[188]. In selected patients, the addition of localized radiation therapy to sites of previously bulky disease or sites with evidence of localized persistent disease documented on FDG-PET scanning may be useful[195]. With currently available supportive care treatment, ASCT-related mortality is expected to be <5%, with the most experienced centres achieving as low as ≤2–3%[188,193,194,196]. Long-term toxicities of major concern after ASCT include near universal infertility in women of >25 years of age and in men of any age; a 5–10% risk of development of second neoplasms; and hypothyroidism[197].

A team of investigators led by the German Hodgkin Study Group developed and validated a prognostic model that is quite useful in predicting the probable outcome in patients undergoing ASCT for recurrent or refractory HL[198]. Five independent factors (time to first relapse after primary treatment <3 months, stage IV disease at relapse, performance status measured with the Eastern Cooperative Oncology Group (ECOG) scale ≥1 at relapse, largest individual tumour ≥5 cm in diameter at relapse, and lack of complete response to second-line chemotherapy) could be combined into a score that identified four prognostic groups: in patients with no risk factors, one factor, two factors and three or more factors, 5-year PFS was 77%, 68%, 57% and 35%, respectively. This model may provide useful guidance to clinicians as they counsel patients with recurrent or refractory HL. More recently, a prognostic model based on gene expression profiling of biopsy tissue from the recurrent tumour has shown promise in identifying a subset of patients with particularly poor outcomes after ASCT, thereby identifying a group in whom experimental approaches may be more appropriate than ASCT[103].

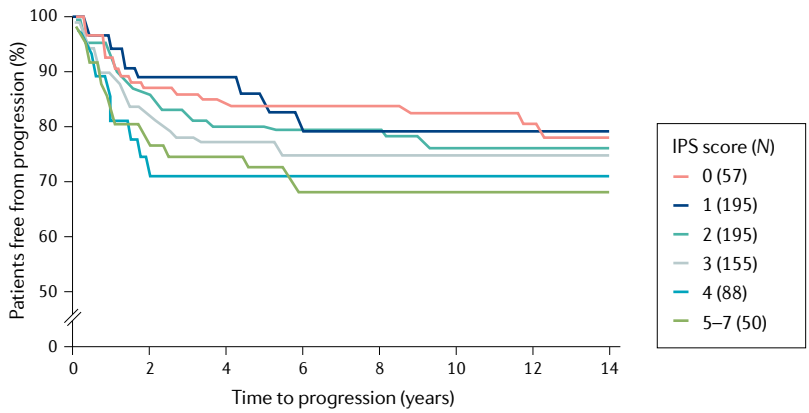

Fig. 8 | **Freedom from progression in Hodgkin lymphoma.** Proportion of patients free from progression over time, according to their International Prognostic Factors Project score (IPS). These 740 patients were treated with Adriamycin (doxorubicin), bleomycin, vinblastine and dacarbazine (ABVD) between 1995 and 2010 in British Columbia. Data from REF.[160].

Special considerations. For three special subgroups, the choice of treatment for recurrent and refractory HL remains controversial. Patients who relapse solely in originally involved but never irradiated lymph nodes and without B symptoms or extranodal disease have a cure rate of 40% to 50% with wide-field radiation therapy[199], and patients who relapse without B symptoms more than 1 year after completion of primary treatment may achieve a cure rate of up to 30% to 40% with additional chemotherapy with or without radiation therapy[195,199]. However, patients in both of these subgroups may achieve a 10-year PFS rate of up to 80% after ASCT with or without radiation therapy[195]. For this reason, many experts recommend ASCT as standard treatment for patients whose HL has persisted or recurred despite primary treatment regardless of the characteristics of the relapse[149,150]. Finally, whether patients with recurrent or refractory disease should proceed to ASCT if they have only a partial response to second-line treatment remains controversial. Many centres advocate an approach in which patients only receive ASCT if they have a complete response to second-line chemotherapy[15,16,188,200–202]. Functional imaging with FDG-PET has proven quite helpful in assessing the quality of response to second-line chemotherapy in this setting. A complete metabolic response to second-line treatment strongly predicts a successful outcome after subsequent ASCT[200–202]. At centres following this approach, patients with less than complete response to second-line chemotherapy are often treated with an alternative third-line regimen or local radiation therapy[195], with the goal of achieving a complete response before proceeding with ASCT. However, other centres recommend proceeding to ASCT regardless of the response to second-line treatment as measured on CT or FDG-PET scan, on the basis that, although a partial response to second-line treatment strongly correlates with a poor outcome after subsequent ASCT, at least 20% to 30% of these patients still can be cured by ASCT[203,204].

New approaches. Attempts to improve the outcomes of ASCT in patients with recurrent or refractory HL have included further intensification of the treatment by

Table 3 | **ABVD versus escalated BEACOPP for advanced-stage Hodgkin lymphoma**

Study	Regimen	EFS (%)	*P*	OS (%)	*P*	Ref.
GISL HD2000	eBEACOPP	69 (10 years)	0.06	85 (10 years)	NS	175
	ABVD	75 (10 years)		84 (10 years)		
GSM-HD	eBEACOPP	78 (7 years)	0.15	89 (7 years)	0.39	178
	ABVD	71 (7 years)		84 (7 years)		
EORTC (HD7) IPS 0–2	e/bBEACOPP 4/4	77 (5 years)	0.07	99 (5 years)	0.06	177
	ABVD	62 (5 years)		92 (5 years)		
EORTC (HD8) IPS 3–7	e/bBEACOPP 4/4	69 (4 years)	0.31	90 (4 years)	0.21	176
	ABVD	64 (4 years)		87 (4 years)		

ABVD, Adriamycin (doxorubicin), bleomycin, vinblastine and dacarbazine; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone; eBEACOPP, BEACOPP with increased doses of etoposide and cyclophosphamide compared with standard doses used for HL; e/bBEACOPP 4/4, chemotherapy consisting of four cycles of escalated BEACOPP followed by four cycles of BEACOPP with standard doses of etoposide and cyclophosphamide; EFS, event-free survival (that is, survival free from progression, relapse or death due to any cause); EORTC, European Organisation for Research and Treatment of Cancer; GISL, Gruppo Italiano Per Lo Studio Dei Linfomi; GSM-HD, Gruppo Italiano di Terapie Innovative nei Linfomi and Intergruppo Italiano Linfomi-Hodgkin disease; IPS, International Prognostic Factors Project score; NS, not significant; OS, overall survival.

providing more than one cycle of high-dose chemotherapy or a second ASCT but have not conclusively identified a successful alternative approach[205–207]. The high cost, much higher treatment-related mortality than that seen with ASCT (by >15%) and the frequent occurrence of symptomatic late-onset toxicity from graft versus host disease have limited the applicability of allogeneic stem cell transplantation to recurrent or refractory HL[208,209]. Despite these limitations, allogeneic stem cell transplantation remains a reasonable option for carefully selected fit, young patients with recurrent HL who have a suitable allogeneic donor, but this technique has limited applicability in the overall management of HL patients.

A major step forward in the management of patients with recurrent or refractory HL was achieved with the addition of consolidation treatment with brentuximab vedotin. The AETHERA trial demonstrated that approximately one-third of the relapses expected to occur after ASCT in patients with recurrent or refractory HL and adverse prognostic factors (relapse or progression <12 months from the end of frontline therapy, HL refractory to frontline therapy, failure to achieve a complete remission after frontline therapy, or extranodal involvement at the time of pre-ASCT relapse) can be eliminated by adding a course of brentuximab vedotin after recovery from the ASCT[186,187,210].

Quality of life

Health-related quality of life (HRQOL), which reflects physical, psychological and social functioning, is impaired in many survivors of HL, who frequently experience high levels of fatigue (30–40% of long-term survivors)[211], decline in cognitive performance (30–40%)[212], impaired sexual function (20–30%)[213] and various other dysfunctions[214]. Although treatment-induced infertility and sexual dysfunction have received particular attention[213], few published studies have addressed other late-onset effects, and many studies lack longitudinal assessment[211]. Fatigue is frequently reported in a relatively high proportion of patients successfully treated for HL who otherwise show normal levels of physical functioning[215–217]. The factors contributing to these undesirable long-term outcomes are poorly understood. Quantifiable, treatment-induced endocrine, immunological and cardiopulmonary abnormalities specifically causing these late-onset complications of HL or its treatment have been postulated but remain unconfirmed. Undoubtedly, psychological changes including emotional distress, depression and anxiety are commonly experienced by survivors of treatment for cancer, including those with HL, and have a role, perhaps by interfering with normal social or emotional functioning, and may be complicated by or lead to inability to return to work[218,219]. At the other end of the age spectrum, HRQOL assessment in elderly patients must address the unique challenges that these individuals experience with advancing age, such as the normal decline in organ function, the effect of comorbid medical conditions and the potentially overlapping toxicity of medications required for unrelated conditions. These additional factors affect daily living and may add additional physical and mental impairments. Attention to this special patient group in recent analyses has shown that a substantial number of these patients still carry a troublesome burden of late-onset impairments even many years after the end of therapy.

HRQOL in patients with HL is undoubtedly affected by long-term complications of treatment, in particular excess overall mortality[161,220], infertility[221,222] and the increased risk of second neoplasms[223–225], all of which have been extensively documented in survivors of HL. The focus on individualizing treatment, avoidance of exposure to alkylating agents, shortened courses of chemotherapy, reduction in field sizes and doses of radiation therapy and omission of radiation therapy in selected patients on the basis of the ability of functional imaging to separate non-malignant residual masses from persistent lymphoma are innovations specifically designed to maintain high levels of effectiveness of HL treatment while reducing the risk of late complications. It is heartening that analyses of evolving standardized mortality in survivors of HL have begun to document improvements in relative survival compared with that observed in the normal population in more recent treatment eras[226,227]. For example, a study using the US Surveillance, Epidemiology, and End Results (SEER) Program database demonstrated that the 10-year relative survival of patients with HL improved from 62.1% to 80.1% between 1980–1984 and 2000–2004. It is reasonable to hope that such improvements in relative survival will translate into improvements in HRQOL.

Measuring HRQOL

Most HL-related HRQOL research has employed cross-sectional approaches and low patient numbers, thereby limiting its usefulness. Further limitations to HL-related HRQOL studies include inadequate recording of patient and treatment history and highly variable follow-up. Interpretation of prospective multicentre trials attempting to use longitudinal data on HRQOL have been challenged by incompleteness of datasets, which

substantially limits the value of the results. Nevertheless, preliminary analyses suggest that HRQOL 2–3 years after completion of therapy is crucial and represents a key assessment point to identify successful recovery or persistence of long-term limitations[228]. Because many very different factors contribute to its complexity, HRQOL in patients with HL has proven difficult to measure. However, there is increasing recognition that the development of effective intervention strategies to improve the survivorship experience among young adults will require concurrent improvement in the tools used to assess short-term and long-term HRQOL in patients. It has become clear that patient-reported outcome (PRO) measures are essential sources of data for assessment of HRQOL[229]. The EORTC Quality of Life Questionnaire C30 (EORTC QLQ-C30) and Functional Assessment of Cancer Therapy (FACT), both of which incorporate PROs, are available in multiple languages, are brief and economical to administer and have emerged as the most suitable cancer-specific core instruments for HRQOL assessment internationally[230,231]. Despite the usefulness of these tools, designing HL-specific HRQOL modules has remained difficult because, unlike other cancers, particular problems unique to HL (such as possible underlying disruption in normal immune function, frequent inclusion of multiple neurotoxic agents in the treatment and disruption of employment during early stages of career development) have defied easy quantification. Fortunately, paediatric oncology investigators have made progress in the development of instruments to measure HRQOL and late-onset effects by focusing on developmental issues in areas such as peer relations, school, family and play[232,233].

It has become clear that measuring HRQOL before, during and after therapy with a follow-up of at least 12 to 18 months and possibly longer is necessary to obtain useful data. Progress in HL therapy is leading to constant growth in the cohort of long-term survivors across several different subgroups, making it clear that new approaches to HRQOL assessment that take into account the particular problems and late-onset complications of each group are needed[234]. Because society-wide changes in daily living circumstances, such as changes in employment and educational opportunities and alterations in availability of supportive care, that occur many years after treatment may have a strong effect on patients' HRQOL, it is also essential to acquire reference data from age-matched and sex-matched healthy populations. Finally, the complexity of factors affecting HRQOL indicates that comprehensive approaches that account for each patient's unique life situation will be necessary for adequate interpretation of study results. Ongoing HRQOL evaluation by the major HL study groups, if properly conducted, should provide the opportunity to improve our study designs and to develop prevention strategies to better support patients on their way back to a normal life.

Outlook

Despite the enormous progress that has been made in understanding and treating HL over the past several decades, ever deepening appreciation of HL basic biology holds the potential to lead to further improvement. Explication of the specific factors causing HL to develop would enable us to identify specific individuals at risk and, therefore, to define efficient strategies for early detection and even prevention. More complete understanding of how malignant HRS cells evade immune detection should lead to the development of more effective, more selective and less toxic interventions employing therapeutic agents specifically targeted at correction of immune dysfunction or direct elimination of the malignant cells while sparing normal cells and tissue. Finally, as improved therapeutic agents and strategies emerge, personalization of treatment based on each individual patient's tumour type and burden as well as pre-existing organ function and comorbid conditions should enable improved matching of specific treatment type and duration with an individual patient's needs. Future prospects for patients with HL remain bright.

Novel diagnostic techniques

The rarity of HRS cells has challenged the application of some of the most powerful biological analytic tools, especially genomic studies, that have provided remarkable insights into the biology, diagnosis and management of cancer since the 2000s. The application of high-throughput genomic sequencing of ctDNA is rapidly transforming our understanding of HL[56,235–239]. Genotyping of ctDNA has revealed new mutations associated with HL and increased our understanding of the frequency with which previously identified mutations occur[56,235,237]. Longitudinal assessment has shown that levels of detectable ctDNA are correlated tightly with persistence of HL during treatment[56,236]. Disappearance of HL-associated ctDNA during treatment with chemotherapy is strongly associated with negative functional imaging (FDG-PET) and increased probability of long-term PFS. For example, in a study of 49 paediatric patients with cHL being treated with chemotherapy, in the 43 patients in whom ctDNA became undetectable, early assessment with FDG-PET scanning demonstrated a complete metabolic response, and in five of the six patients with persistence of disease on FDG-PET scan, ctDNA remained detectable[235]. Longitudinal sampling has also shown clonal evolution of HL in patients whose HL has persisted during treatment, with low-level ancestral clones (that is, clones of tumour cells that were present at diagnosis) becoming dominant and new mutations emerging in patients being treated with the immune checkpoint inhibitor nivolumab (a monoclonal antibody to PD1)[56]. Finally, patients with complete responses to chemotherapy and long-term PFS have a larger decrease in the level of detectable ctDNA after just two cycles of ABVD than patients who eventually relapse[56]. These and similar observations indicate that measurement of ctDNA is contributing to improved understanding of the biology of HL and has the potential to complement the prognostic utility of interim and end-of-treatment FDG-PET scanning.

Incorporating novel agents

After decades of fine-tuning the treatment of HL to minimize toxicity while maintaining efficacy by using lower doses and smaller fields of radiation and fewer

cycles of chemotherapy, new drug approvals have the potential to transform our approach to the treatment of HL with a realistic expectation of improved outcomes in even the patients at the highest risk. Currently, the primary challenge is to understand how and when to incorporate novel, highly active agents such as brentuximab vedotin, nivolumab and pembrolizumab (a monoclonal antibody to PD1) into the treatment paradigm. Outstanding questions include whether they should be added to or replace drugs in existing regimens, serve as the backbone for new combinations, be employed in the primary or recurrent and refractory setting and be explored predominantly in the patients at the highest risk or in all stages and prognostic groups. Evaluation of these promising new agents is complicated by lack of reproducible predictive and prognostic markers, the difficulty in defining meaningful end points in a disease in which current 5-year OS is as high as 90%, the relatively small patient numbers, which make it impractical to test multiple iterations of innovative regimens, and the need to assess the potential economic burden of expensive novel therapies. Despite these questions and concerns, there is much reason for optimism as we unravel the intricacies of the biology of HL and use this knowledge to develop new targeted approaches.

Brentuximab vedotin. The FDA initially approved brentuximab vedotin in 2011 for the treatment of patients with cHL that had relapsed after prior treatment with ABVD and high-dose chemotherapy, on the basis of an overall response rate of 75% and complete response rate of 34%[184]. Since then, results of two large phase III studies quickly expanded the indications to maintenance therapy following ASCT[186] and as primary therapy in combination with AVD in patients with stage III or IV disease (ECHELON-1 trial)[65]. Interpreting and applying the results of the ECHELON-1 trial exemplifies the often challenging treatment decisions faced in HL. The modest (albeit statistically significant) improvement in 2-year PFS with the substitution of brentuximab vedotin for bleomycin in the ABVD regimen (82.1% compared with 77.2% in the standard ABVD arm) came at a price, including more frequent peripheral neuropathy and febrile neutropenia, which resulted in the recommendation to use primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) in all patients[65]. The increased pulmonary toxicity noted with the ABVD regimen will probably be mitigated by eliminating bleomycin from the last four cycles of treatment in the 80% of patients with a negative interim FDG-PET scan[240]. In an economic analysis of the ECHELON-1 study, the incremental cost-effectiveness ratio (ICER) of brentuximab vedotin and AVD was US$317,254 per quality-adjusted life year (QALY), more than twice the threshold often used to determine the economic feasibility of new interventions (lifetime health-care costs for brentuximab vedotin–AVD were estimated at US$361,137, compared with US$184,291 for ABVD), but could be reduced to an acceptable range with a substantial decrease in the high retail drug price (a price reduction of 56% for brentuximab vedotin would reduce the ICER to US$150,000 per QALY)[241]. Based on concerns related to toxicity and perhaps cost, and without a survival benefit at this early 2-year time point, AVD in combination with brentuximab vedotin has not yet been widely adopted as the standard of care for all patients with advanced-stage disease, but it is gaining favour in high-risk patients (patients with stage IV disease or extranodal involvement at two or more sites)[65], in whom subgroup analysis suggested the greatest benefit. Longer follow-up will be essential in assessing the overall benefit of this regimen.

Another question is whether a different schedule and fewer doses of brentuximab vedotin in combination with AVD would result in a similar improvement in PFS with a more favourable toxicity profile and lower cost. In a phase II study of patients of ≥60 years of age with newly diagnosed HL, brentuximab vedotin was administered as a single-agent for two cycles, followed by six cycles of AVD and then four additional consolidation doses of single-agent brentuximab vedotin[242]. The 2-year PFS and OS rates were 84% and 93%, respectively, which are unprecedented results in this elderly high-risk population. Febrile neutropenia occurred in 8% of patients, G-CSF was administered to 40% of patients (to 15% as primary prophylaxis and to 25% as secondary prophylaxis), and 33% of patients experienced grade 2 peripheral neuropathy. Efforts to use brentuximab vedotin alone or in combination with dacarbazine or bendamustine as initial therapy in elderly patients have been less successful owing to high rates of relapse or unacceptable toxicity[243].

Combinations of brentuximab vedotin with standard salvage regimens such as ICE or etoposide, methylprednisolone, cytarabine and cisplatin (ESHAP) and bendamustine, given either sequentially or concurrently, are under investigation as treatment for recurrent or refractory disease[244–246]. Without randomized trials, the benefit of adding brentuximab vedotin in the pre-ASCT setting is hard to quantify. If use of brentuximab vedotin expands in the primary setting, the expectations for the drug in subsequent lines of therapy would be more limited, although high rates of response to re-treatment with single-agent brentuximab vedotin have been reported in a small number of patients with recurrent disease[247].

PD1 inhibitors. The recent Nobel Prize-winning discovery of PD1, a negative immune regulator on T cells, established a new principle for cancer therapy[248]. Unleashing the immune system with PD1 inhibitors such as nivolumab and pembrolizumab has resulted in remarkable responses in a number of refractory malignancies including HL[249,250]. Although severe autoimmune complications have been reported in a small percentage of patients, overall the treatment is extremely well tolerated and can be safely administered for extended periods of time.

As with brentuximab vedotin, the high single-agent activity of the PD1 inhibitors has stimulated interest in combination therapies, in both the primary and recurrent setting. The preliminary results of a phase II trial of nivolumab and AVD in patients with advanced-stage newly diagnosed HL (Checkmate 205 clinical trial) are encouraging[251]. Patients received four doses of nivolumab monotherapy followed by six cycles

of nivolumab and AVD, with an overall response rate of 84% (67% complete response) and a 9-month modified PFS of 92%. The treatment was well tolerated, although G-CSF supportive therapy was used as secondary prophylaxis in the majority of patients. A phase III North American Intergroup trial comparing brentuximab vedotin and AVD with nivolumab and AVD in patients with previously untreated advanced-stage HL is now open (ClinicalTrials.gov NCT03907488).

Combinations of novel agents. The combination of nivolumab and brentuximab vedotin for use in the recurrent setting is considered very promising and is also under investigation as primary therapy in elderly patients (NCT02758717). A phase II study of this combination as second-line therapy found an overall response rate of 82% and a complete response rate of 61%, with <10% of patients requiring systemic steroids for immune-related adverse events[252]. Stem cell mobilization and engraftment of the subsequent ASCT were not compromised by the regimen. The combination of brentuximab vedotin, nivolumab and ipilimumab (a monoclonal antibody to cytotoxic T lymphocyte protein 4 (CTLA4)) in a heavily pretreated population showed responses in 95% of patients, with 84% complete responses[253]. A large randomized phase II study (NCT01896999) is underway comparing the combination of brentuximab vedotin, nivolumab and ipilimumab with brentuximab vedotin and nivolumab in recurrent disease.

In the pipeline

In addition to brentuximab vedotin and the PD1 inhibitors, the other agents with unique mechanisms of action that seem to show early promise in refractory HL are camidanlumab tesirine and CAR T cells. Camidanlumab tesirine is an antibody–drug conjugate (ADCT-301) composed of a monoclonal antibody to CD25 (camidanlumab) linked to a pyrrolobenzodiazepine drug (tesirine); the conjugate showed an 80.8% overall response rate with a 50% complete response rate with durable remissions in a highly pretreated population of patients, and a phase II study is in development[254]. Importantly, severe autoimmune neurotoxicity including Guillain-Barré syndrome has been reported in a few patients and may limit use of the drug to the heavily pretreated, refractory setting.

In contrast to the rapid FDA approval of CAR T cells for the treatment of relapsed B cell acute lymphoblastic leukaemia and diffuse large B cell lymphoma, the development of CAR T cells for the treatment of HL has been slower, but this approach will probably become a viable option over the next several years[255,256]. Autologous CAR T cells that target CD30 are under investigation in heavily pretreated patients with HL[257–259]. The first trial found a partial response in 39% of 18 patients, with a median PFS of 6 months[257]. In another trial the addition of lymphodepleting chemotherapy before CAR T cell infusion, as has been done in non-Hodgkin lymphoma, resulted in a substantial improvement in efficacy with complete responses lasting >9 months in six of nine patients[258,259].

Conclusions

With brentuximab vedotin and PD1 inhibitors joining the armamentarium, the treatment of HL continues to be a remarkable success story. Current efforts to incorporate these agents in all stages and lines of therapy while maintaining our enduring goal of maximizing efficacy while minimizing acute and late-onset toxicities will undoubtedly result in improved outcomes. These efforts will be strengthened by the ongoing extraordinary laboratory work to understand the survival mechanisms of HRS cells and the complex interactions with the TME. As with PD1 inhibitors, these discoveries have the very real potential for identifying new therapeutic targets in HL. Ideally, improved predictive and prognostic markers will be identified to enable us to determine which patients are most likely to benefit from these novel and often costly approaches.

Published online: 23 July 2020

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Author contributions

Introduction (J.M.C.); Epidemiology (W.C., A.C. and J.M.C.); Mechanisms/pathophysiology (C.S., A.C. and J.M.C.); Diagnosis, screening and prevention (A.C., W.C., C.S. and J.M.C.); Management (R.T.H., N.L.B. and J.M.C.); Quality of life (H.-H.F. and J.M.C.); Outlook (N.L.B. and J.M.C.); Overview of Primer (J.M.C.).

Competing interests

J.M.C. has received research support and honoraria from Seattle Genetics and Takeda Pharmaceuticals; N.L.B. has received research support from Seattle Genetics, Takeda Pharmaceuticals, Bristol-Myers Squibb and Merck, and is on the Advisory Board of ADC Therapeutics and Seattle Genetics. All other authors declare no competing interests.

Peer review information

Nature Reviews Disease Primers thanks P. Borchmann, L. Castagna, A. Gallamini, R. Jarrett, R. Küppers, A. Sureda and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.

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